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PLASMA CONCENTRATIONS AND PROTEIN BINDING OF DISOPYRAMIDE AND MONO-*N*-DEALKYLDISOPYRAMIDE DURING CHRONIC ORAL DISOPYRAMIDE THERAPY

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1 The plasma levels of disopyramide and mono-*N*-dealkyldisopyramide were measured from 118 patients, and the protein binding of both drugs from 50 patients during chronic oral disopyramide therapy.

2 No significant correlation was seen between the daily dose of disopyramide and the achieved plasma drug concentration.

3 The concentration of mono-*N*-dealkyldisopyramide in the plasma was about one third of that of disopyramide in patients with normal renal function.

4 The mean plasma levels of disopyramide and mono-*N*-dealkyldisopyramide were high in patients with renal impairment. In patients with simultaneous therapy with enzyme inducing drugs the mean levels of disopyramide were low and those of mono-*N*-dealkyldisopyramide high.

5 In patients with effective treatment of ventricular arrhythmias the levels of disopyramide were significantly higher than in those with ineffective treatment; the difference was not significant in supraventricular arrhythmias. Patients with side-effects had slightly though not significantly higher disopyramide levels than patients without side-effects; mono-*N*-dealkyldisopyramide concentrations were identical.

6 The average protein binding of disopyramide was 82%, and that of mono-*N*-dealkyldisopyramide 22–35%. Although a concentration dependent binding of disopyramide was seen within an individual, the average protein binding did not vary significantly at different concentrations of all samples analyzed. The protein binding was not altered in renal insufficiency, but was slightly decreased by high concentrations of mono-*N*-dealkyldisopyramide.

Introduction

The antiarrhythmic agent, disopyramide, has been in clinical use since the late 1960s. During this time it has been a subject of extensive clinical and experimental study. It has proved effective in various types of supraventricular and ventricular arrhythmias (e.g. Smith, 1978) and safe in therapy of up to five years' duration (Yu, 1979).

Little is known about mono-*N*-dealkyldisopyramide, the major metabolite of disopyramide, especially about its clinical significance. In animals it is more anticholinergic than disopyramide, and it has both antiarrhythmic and inotropic effects (Grant, Marshall & Ankier, 1978).

There seems to be a relationship between the antiarrhythmic activity and serum levels of disopyramide (Rangno, Warnica, Ogilvie, Kreeft & Bridger, 1976; Niarchos, 1976; Oshrain, Laidlaw, Cook & Willis, 1976; Smith, 1978). A remarkably constant ratio between plasma and myocardial disopyramide concentrations in dogs was recently demonstrated by Patterson and coworkers (Patterson, Stetson & Lucchesi, 1979). The reported therapeutic plasma or serum level ranges of disopyramide have varied, but according to a recent review by Koch-Weser (1979) the levels of 2–5 μg/ml seem to represent the usually effective therapeutic range. Concentrations above 7 μg/ml appear to carry a considerable risk of toxicity.

It has been suggested that free disopyramide concentration might be a better index for dosage adjustments than the total plasma concentration (e.g. Koch-Weser, 1979). However, information about the degree of the protein binding of disopyramide has varied considerably (see Heel, Brogden, Speight & Avery, 1978).

The purpose of the present investigation was to

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study factors affecting the plasma concentrations of disopyramide and its main metabolite achieved during conventional oral disopyramide therapy. In order to consider the significance of measuring drug levels during disopyramide therapy, an effort was also made to elucidate the possible relationship between therapeutic efficacy or side-effects and plasma levels of disopyramide and mono-*N*-dealkyldisopyramide.

Methods

The aim was to determine disopyramide (DIS) and mono-*N*-dealkyldisopyramide (MND) plasma concentrations from all patients receiving oral disopyramide therapy in the Department of Medicine, University of Turku, Finland, at steady state (after no less than two days after starting disopyramide therapy). The total number of patients in the series was 118, that of separate determinations 173. For various reasons, only part of the determinations could be used in different analyses: (1) For statistical reasons, only the first determinations of any patient were included when the dependence of plasma concentration on dose, renal function, age, simultaneous therapy, or duration of therapy was studied, and also when the efficacy of therapy was estimated. So later samples from the same patients were only included when side-effects were studied. (2) Only results from drug plasma concentration determinations, where all four determinations (disopyramide at 0 h (before the next dose) and 2 h (2 h after the dose), MND at 0 h and 2 h) were successfully completed, were included in the analyses (on several occasions e.g. one of the samples was missing, and on some occasions an analysis was not successful because of e.g. interfering peaks in the assay). (3) In some cases the hospital records did not give all information needed, e.g. weight or serum creatinine level of the patient. When therefore calculation, or group allocation was not possible, the patient was excluded. (4) When all time intervals of the ECG could not be measured (e.g. technical difficulties, atrial fibrillation) before and during disopyramide therapy, the patient was excluded from time interval studies. The patient analysis was retrospective and was based solely on routine hospital records.

The efficacy of disopyramide treatment was estimated from the registered ECGs of the patients. Generally a routine 12 lead ECG was recorded, 3 leads simultaneously, for approximately 8 s, so an ECG of altogether about 30 s duration was available before and during disopyramide therapy. When no arrhythmia was seen in the ECG thus obtained during disopyramide treatment, the therapy was considered efficient.

Electrocardiographic time intervals were measured

Table 1 Effects of renal impairment and drug metabolizing enzyme activities inducing drugs on the plasma levels of disopyramide and mono-*N*-dealkyldisopyramide. Means ± s.e. mean have been indicated.

			Normal renal function		
	Renal impairment ($n = 17$)		*No inducers* ($n = 63$)		*Inducers* ($n = 7$)
Age (years)	67.4 ± 1.9	*	61.7 ± 1.2	NS	55.1 ± 5.6
Creatinine (μmol/l)	181 ± 16 (125 – 402)	***	92.5 ± 1.7	NS	93 ± 5.6
Daily dose					
(mg)	429 ± 25	NS	438 ± 15	NS	457 ± 37
(mg/kg)	5.54 ± 0.03	NS	6.01 ± 0.20	NS	6.95 ± 0.57
Drug concentrations (μg/ml)					
DIS 0 h	3.57 ± 0.36	*	2.85 ± 0.14	*	1.67 ± 0.38[1]
DIS 2 h	4.29 ± 0.41	NS	3.27 ± 0.16	**	1.86 ± 0.22[2]
MND 0 h	1.41 ± 0.19	**	0.84 ± 0.06	+	1.72 ± 0.36[1]
MND 2 h	1.49 ± 0.21		0.99 ± 0.06	+	2.03 ± 0.38
MND/disopyramide concentration ratio					
0 h MND/DIS	0.52 ± 0.15	NS	0.34 ± 0.03	*	1.21 ± 0.26
2 h MND/DIS	0.41 ± 0.09		0.29 ± 0.02	*	1.24 ± 0.31

[1] $n = 6$; [2] $n = 5$.

NS = $P>0.1$; + = $P<0.1$; * = $P<0.05$; ** = $P<0.01$; *** = $P<0.001$.

before disopyramide treatment and during therapy at the same time as the blood samples were collected. QT was corrected to pulse rate 60 according to Bazett (1918–20). The patients were not questioned for side-effects of the therapy, so only side-effects spontaneously complained of were recorded. All other medication used by the patients was recorded.

Drug analyses

Blood samples were collected into tubes containing EDTA, plasma was separated by centrifuging, and the samples were stored frozen until assayed. Each plasma sample was analyzed for disopyramide and mono-*N*-dealkyldisopyramide in two replicates by a gas chromatographic method (Aitio, 1979). The protein binding of disopyramide and mono-*N*-dealkyldisopyramide was determined by equilibrium dialysis at 37°C (Virtanen, 1981). For protein binding 69 samples from 50 patients were analyzed.

Table 2 Effect of prolonged disopyramide therapy on the plasma concentrations of disopyramide and mono-*N*-dealkyldisopyramide. Means ± s.e. mean are indicated.

	Duration of treatment		
	Under 10 days		*10 days or over*
n	46		17
Age (years)	62.8 ± 1.2	NS	58.5 ± 2.8
Creatinine (μmol/l)	94.0 ± 2.0	NS	88.7 ± 3.0
Dose (mg)	430.0 ± 18	NS	459.0 ± 27
(mg/kg)	6.05 ± 0.24	NS	6.22 ± 0.36
Plasma drug levels (μg/ml)			
DIS 0 h	3.00 ± 0.17	+	2.45 ± 0.24
DIS 2 h	3.92 ± 0.20	*	3.20 ± 0.22
MND 0 h	0.85 ± 0.07	NS	0.82 ± 0.10
MND 2 h	0.98 ± 0.07	NS	0.99 ± 0.12

NS = $P>0.1$; + = $P<0.1$; * = $P<0.05$

Statistical analyses

When comparing two interdependent series, the Student's *t*-test for paired observations was used. In comparisons of independent series, the variances were first studied with F test. If the variances were not significantly different, the Student's *t*-test was applied, otherwise the approximate test of Welch was used. Two tailed tests were used every time. The significance of correlations were tested using the ordinary parametric test, or the Spearman's rank correlation test, when indicated. The statistical significances have been denoted as follows: $P<0.001$ =***, highly significant, $P<0.01$ =**, significant, $P<0.05$ =*, almost significant, $P>0.05$ = NS, not significant.

Results

(a) *Factors affecting the concentrations of disopyramide and MND in the plasma*

There were 63 patients with normal renal function (serum creatinine under 120 μmol/l), who were not simultaneously using enzyme inducing drugs. The regression between the daily dose (in mg/kg and mg) and the plasma concentrations of disopyramide were statistically not significant (DIS 0 h $r = 0.073$, 2 h $r = 0.150$ (dose calculated in mg), and DIS 0 h $r = 0.011$, DIS 2 h $r = 0.125$ (dose calculated in mg/kg)). On the other hand, the correlation between dose of disopyramide and the plasma concentration of MND was significant, although not very good (MND 0 h $r = 0.234$, NS, MND 2 h $r = 0.311$, $P<0.05$, (dose calculated in mg), MND 0 h $r = 0.301$, $P<0.05$, MND 2 h $r = 0.481$, $P<0.001$ (dose calculated in mg/kg). The plasma drug levels achieved can be seen in Table 1. The amount of MND in the plasma was about one third of that of disopyramide. In this respect the individuals displayed a continuous variation, with highest and lowest MND/DIS ratios of 1.3 and 0.07, respectively.

Table 3 Disopyramide and MND concentrations in patients with effective and not effective arrhythmia treatment. Effective treatment was defined as disappearance of the original arrhythmia, ineffective as continuance of the arrhythmia (with increased, decreased or unchanged intensity). Means ± s.e. mean are indicated.

	Supraventricular arrhythmias			*Ventricular arrhythmias*		
	Effective		*Ineffective*	*Effective*		*Ineffective*
n	14		13	50		31
DIS 0 h	3.19 ± 0.36	NS	2.75 ± 0.37	3.14 ± 0.17	**	2.32 ± 0.27
DIS 2 h	3.66 ± 0.52	NS	3.27 ± 0.45	3.99 ± 0.21	*	3.29 ± 0.26
MND 0 h	0.92 ± 0.19	NS	1.03 ± 0.14	0.93 ± 0.08	NS	1.09 ± 0.14
MND 2 h	1.19 ± 0.21	NS	1.13 ± 0.23	1.04 ± 0.08	NS	1.25 ± 0.14

NS = $P>0.05$; * = $P<0.05$; ** = $P<0.01$

Table 4 Effect of disopyramide therapy on time intervals measured from the ECG of 82 patients. Means ± s.d. are indicated.

Time interval (ms)	*Control*	*Treated*	P
QRS	89 ± 22	90 ± 21	NS
PR	170 ± 31	171 ± 34	NS
ST	286 ± 43	302 ± 38	<0.001
Corrected QT[1]	423 ± 55	437 ± 49	<0.01
Heart rate (beats/min)	79.0 ± 20.2	76.2 ± 15.0	

[1] QT was corrected to heart rate 60 according to the formula

$QT_{corrected} = QT_{measured} \times \sqrt{\text{heart rate}/60}$ (Bazett 1918–20)

The serum creatinine level was above normal in 18 patients (range 125–1297 μmol/l). The patient with creatinine level of 1297 μmol/l was excluded from Table 1 because his renal function was so widely different from that of all the others. The mean plasma levels of disopyramide and MND of patients with renal insufficiency were slightly higher than those in patients with normal renal function and the variation in both disopyramide and MND was wider. The MND/DIS ratio was also higher, but the differences was not statistically significant (Table 1). The correlation between the plasma concentrations per drug dose and serum creatinine was significant only for MND. (DIS 0 h $r = 0.019$, NS, DIS 2 h $r = 0.443$, NS, MND 0 h $r = 0.730$, $P<0.001$, MND 2 h $r = 0.784$, $P<0.001$). The corresponding rank correlations calculated according to Spearman were all nonsignificant.

Seven patients with normal renal function were using enzyme inducing drugs simultaneously (one or two together, including diphenylhydantoin 5, carbamazepine 2, spironolactone 2). The plasma levels of disopyramide were significantly lower than those of the 'no inducers-group'. The mean levels of MND in these patients (Table 1) were about twice those of the control group ($P<0.1$). Respectively, the MND/DIS ratio was higher ($P<0.05$).

The effect of prolonged disopyramide treatment on plasma drug levels was studied by comparing patient groups with disopyramide therapy longer/shorter than 10 days. Disopyramide levels seemed to be lower after 10 days' therapy, whereas no difference was seen in MND levels (Table 2).

(b) Efficacy of disopyramide treatment

In patients whose supraventricular arrhythmias were effectively treated, the disopyramide mean 0 h plasma level was 3.19 ± 0.36 μg/ml, in those with ineffective therapy 2.75 ± 0.37 μg/ml (Table 3). The difference was not significant. In the patient group with ventricular arrhythmias there was a significant difference in disopyramide 0 h plasma levels between effective treatment (3.14 ± 0.17 μg/ml) and ineffective treatment (2.32 ± 0.27 μg/ml). MND concentrations were similar in effective and ineffective treatment in both groups (Table 3). In ventricular arrhythmias when plasma disopyramide level (0 h) was below 2 μg/ml the therapy was effective in three cases, ineffective in ten cases. At the drug level 2–3 μg/ml the therapy was effective in ten cases, ineffective in eleven cases, at 3–4 μg/ml effective in four, ineffective in three, and at over 4 μg/ml effective in six, ineffective in five cases.

Disopyramide therapy significantly increased the duration of QT interval in the ECG, but had no effect on other parameters (Table 4).

The side-effects complained by the patients were mainly anticholinergic including dry mouth (17), problems in urination (8), gastrointestinal disturbances (14), blurred vision (4), fatigue (7), dizziness and related disorders (7), rash (1), and bradycardia (1). Because of side-effects the therapy was discontinued in 8 cases. From altogether 142 plasma level determinations 33 were recorded with one or several side-effects. Disopyramide plasma levels in patients with side-effects were higher (3.2 ± 0.2 (0 h) and 4.0 ± 0.3 (2 h) μg/ml) than in those without side-effects (2.7 ± 0.1 and 3.5 ± 0.2 μg/ml, respectively.) The difference was not statistically significant ($P<0.1$ for 0 h, NS for 2 h). The concentrations of MND were identical in both groups.

(c) Protein binding of disopyramide and MND

The protein binding of disopyramide and MND at different plasma drug concentrations is presented in Tables 5 and 6. The concentration range of disopyramide was 1.2 to 8.3 μg/ml, and that of MND 0.4 to 5.6 μg/ml. For disopyramide the fraction bound varied between 0.63 and 0.96 (mean 0.82, median 0.83, s.d. of mean 0.07), for MND between 0.0–0.67. The difference in the fraction of DIS bound to protein between the lowest and highest total concentration group was not significant. The binding of DIS in patients with renal insufficiency (creatinine 132–1297 μmol/l, $n = 19$) was 0.80 ± 0.02, that of MND 0.29 ± 0.05 (s.e. mean). The binding of disopyramide

Table 5 Protein binding of disopyramide at different plasma drug levels. Means ± s.e. mean have been indicated

Disopyramide concentration (μg/ml)	*Fraction bound*	
1.2–2.0 (1.65 ± 0.07) $n = 12$	0.82 ± 0.02	NS
.1–3.0 (2.66 ± 0.09) $n = 13$	0.79 ± 0.02	
3.1–4.0 (3.55 ± 0.07) $n = 17$	0.82 ± 0.02	
4.1–5.0 (4.6 ± 0.07) $n = 16$	0.82 ± 0.02	
5.1–6.0 (5.48 ± 0.08) $n = 6$	0.81 ± 0.01	
6.1–8.3 (7.45 ± 0.44) $n = 4$	0.75 ± 0.04	

NS = $P>0.05$

decreased when the concentration of MND increased ($P<0.01$). (Table 7). The unbound fraction of disopyramide was significantly ($P<0.01$) smaller in the 0 h than in the 2 h samples of the ten patients studied (Figure 1).

Discussion

Disopyramide therapy of the present patients was guided by their clinical situation only. In the group of patients with normal renal function there was a wide scatter of disopyramide levels achieved by a disopyramide dose: the correlations between the daily dose (either in mg or in mg/kg body weight) of disopyramide and the plasma concentrations of disopyramide were not statistically significant. Almost all subjects in the present series were patients in a hospital ward. Therefore compliance to therapy probably was very good. Thus it is obvious that disopyramide plasma levels in an individual patient cannot be reliably estimated from the dose. It might be due to the nonlinear pharmacokinetics of disopyramide suggested e.g. by Meffin, Robert, Winkle, Harapat, Peters & Harrison (1979).

In the patients with renal failure the plasma drug concentrations were higher than in the group with normal renal function, but showed a considerably wider variation (Table 1). Whiting & Elliott (1977) have previously reported that the elimination half-life of disopyramide is prolonged in renal failure. No studies are available about the kinetics of MND in renal impairment. Although the correlation between MND concentration/dose and creatinine level was good, it was very poor for disopyramide. Mere creatinine level thus cannot be used in calculating the dose decrement needed in patients with renal failure.

Table 6 Protein binding of mono-*N*-dealkyldisopyramide at different plasma drug levels. Means ± s.e. mean have been indicated.

Mono-N-dealkyldisopyramide concentration (μg/ml)	*Fraction bound*	
0.04–1.0 (0.72 ± 0.06) $n = 15$	0.34 ± 0.05	
1.1–1.5 (1.28 ± 0.03) $n = 17$	0.35 ± 0.03	NS
1.6–2.0 (1.78 ± 0.03) $n = 13$	0.22 ± 0.04	*
2.1–3.0 (2.63 ± 0.05) $n = 7$	0.23 ± 0.06	NS
3.1–5.6 (3.77 ± 0.31) $n = 9$	0.22 ± 0.06	NS

NS = $P>0.05$; * = $P>0.05$

There were three patients with renal failure in whom the MND/DIS ratio was = 1.0 (up to 2.9). The 24 h urine was analyzed from one of these patients, and the ratio was even higher in the urine. Thus the high MND/DIS ratio was not a result from reduced clearance of MND in renal insufficiency.

The simultaneous treatment with an enzyme inducing drug decreased the mean disopyramide concentrations and increased those of MND, and thus the MND/DIS ratio. (Table 1). The enhanced metabolism of disopyramide by enzyme induction was previously demonstrated in rat (Aitio & Aitio, 1979) and recently in man (Aitio & Vuorenmaa, 1980; Aitio, Mansury, Tala, Haataja & Aitio, 1980).

Treatment with disopyramide for more than 10 days caused a slight decrease in the concentrations of disopyramide, but not a concomitant increase in the concentrations of MND. This finding thus neither proves nor excludes enzyme induction by disopyramide.

In the estimation of the efficacy of disopyramide therapy the difference in disopyramide plasma con-

Table 7 Plasma protein binding of disopyramide (DIS) in patients with high plasma levels of mono-*N*-dealkyldisopyramide (MND). Means ± s.e. mean have been indicated

Concentration of DIS (μg/ml)	*Fraction DIS bound*		*Concentration of MND (μg/ml)*
1.5–7.6 (3.10 ± 0.45) $n = 15$	0.82 ± 0.02	**	1.5–2.4 (1.74 ± 0.04)
1.3–8.3 (3.98 ± 0.50) $n = 15$	0.76 ± 0.01		2.5–5.6 (3.28 ± 0.24)

** $P<0.01$

centrations between effective and ineffective treatment was insignificant in supraventricular arrhythmia and small though significant in ventricular arrhythmia. This study was not originally planned so that accurate estimation of efficacy would have been possible. The time used for ECG recording was all too short to securely establish a disappearance of arrhythmia. In the study of Oshrain *et al.* (1976) the mean plasma level of disopyramide in responders and nonresponders was identical. However, it seems according to our data that the plasma levels below 2 μg/ml are rather ineffective. The prolongation of ST and QT intervals following disopyramide treatment was significant. QT prolongation has been used in concentration-effect relationship studies of disopyramide (Bryson, Whiting & Lawrence, 1978; Whiting, Holford & Sheiner, 1980). In these studies drug concentration changes were directly related to QT changes.

The difference between the disopyramide levels causing and not causing side-effects was minor. Mild side-effects like dry mouth seem to occur at very moderate disopyramide levels. There was no difference in the concentrations of MND between the groups with and without side-effects. This is worthy of consideration, because in animals the relative anticholinergic activity of MND was 24 times that of disopyramide (Baines, Davies, Kellet & Munt, 1976).

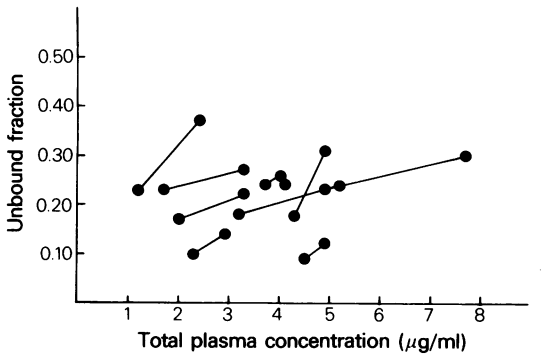

Figure 1 Relationship between total and free plasma disopyramide concentrations in ten patients. Every pair of two interconnected points refers to two separate determinations in a single patient.

Reports about the extent of protein binding of disopyramide show a considerable variation. Chien, Lambert & Karim (1974) reported a 30% binding of disopyramide. Hinderling, Bres & Garrett (1974) showed the bound fraction of disopyramide to increase from 5 to 65% as the total plasma concentration decreased from 72 μg/ml to 0.04 μg/ml. The fraction of MND bound varied from 0.05 to 0.10. High concentrations (150 μg/ml) of the metabolite lowered the binding of disopyramide. Meffin *et al.* (1979) reported the free fraction of disopyramide to be 0.19 to 0.46 over the range of total plasma concentrations of 2–8 μg/ml. All these binding experiments were done *in vitro*, whereas in the present study the samples analyzed were true plasma samples from disopyramide treated patients. However, our results agree very well with those of Meffin *et al.* (1979). The means of the bound fraction of disopyramide were essentially similar at plasma drug concentrations below 2, and over 6 μg/ml. Instead, a trend to a lower binding of MND was seen at higher total drug concentrations. Renal impairment did not change the protein binding of disopyramide or MND. The decrease of the protein binding of disopyramide with increasing concentrations of MND is in accordance with the findings of Hinderling *et al.* (1974). The change was minor, and MND concentrations in excess of 2.5 μg/ml occur infrequently in clinical practice.

The protein binding of disopyramide showed a wide inter-individual variation. This was previously reported also by Meffin *et al.* (1979). Though the average bound fractions of disopyramide did not vary at different concentration levels, the concentration dependence of the binding within subjects can be readily seen from Figure 1.

Because of both interindividual and concentration dependent variation, the free, pharmacologically active concentrations of disopyramide cannot be estimated from total concentrations totally accurately. The variation in the protein binding at different concentration ranges was not very marked. Thus for practical purpose, in general, total concentrations might be used, and maybe a determination of the free fraction can be considered on special occasions.

The cardiac activity of MND has been estimated to be about one fourth of the activity of disopyramide in experimental animals (Grant *et al.* 1978); on the other hand the protein binding of MND is only about one third–one fourth of that of disopyramide. The net effect therefore would tend to be that disopyramide

and MND have about equal cardiac effects, when their total plasma concentrations are similar.

The correlation between the daily dose and concentration of disopyramide and MND is poor, both in normal and abnormal renal function. Especially among patients with renal impairment there seem to be exceptional individuals in whom the plasma concentration of disopyramide is difficult to predict. The metabolism of disopyramide seems to be sensitive to drugs causing induction of drug metabolizing enzymes.

Consequently, determination of disopyramide plasma level can be recommended in guiding disopyramide therapy. Determination of MND might prove useful in patients with renal impairment, or in patients receiving simultaneous therapy with inducing drugs.

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