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THE EFFECT OF ENZYME INDUCTION ON THE METABOLISM OF DISOPYRAMIDE IN MAN

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1 The effects of rifampicin, phenytoin, and disopyramide treatments on the metabolism of disopyramide were studied in patients and volunteers.

2 Rifampicin treatment markedly increased the metabolism of disopyramide.

3 Phenytoin had effects similar to those of rifampicin. The effect subsided in 2 weeks after stopping the treatment.

4 The metabolism of disopyramide seemed fastest in the patient group with the highest dose of disopyramide. Both in patients and volunteers a significant increase occurred in the urinary mono-*N*-dealkyldisopyramide/disopyramide ratio during the first week of disopyramide therapy. This change can partly be due to pharmacokinetic differences between disopyramide and its metabolite. The inducing effect of disopyramide remained uncertain.

Introduction

Disopyramide, a new anti-arrhythmic agent, is excreted predominantly unchanged in the urine. The main metabolic pathway in man is *N*-dealkylation, and approximately 25% of the dose is excreted as mono-*N*-dealkyldisopyramide (MND) in the urine of healthy volunteers (Karim, 1975). The amount of MND in the plasma after a single dose is generally low; during long term therapy the levels of MND reach about 1 μg/ml. Some patients were found, however, whose plasma concentrations of MND were even higher than those of disopyramide (Aitio & Vuorenmaa, 1980). In rat disopyramide *N*-dealkylation can be strongly induced by phenobarbitone, and weakly by disopyramide itself (Aitio & Aitio, 1979).

The purpose of this study was to examine to which extent enzyme induction can affect the metabolism of disopyramide in man. The most extensive study was done with rifampicin, one of the most potent drugs causing enzyme induction, but we also tested whether phenytoin, also used as an antiarrhythmic, can cause this same phenomenon. An effort was in addition made to elucidate the possible enzyme inducing capacity of disopyramide itself.

Methods

Rifampicin study

Twelve patients, seven males and five females, aged 30 to 59 (mean 44.1) years, with newly diagnosed tuberculosis participated in the study with rifampicin. The patients received disopyramide as a single dose (200 mg when weighing below 70 kg and 300 mg when more) before the therapy for tuberculosis was started. The therapy was composed of rifampicin combined with one or two other chemotherapeutic agents (isoniazid, pyrazinamide, ethambutol). After 2 weeks of tuberculostatic therapy the disopyramide

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dose was repeated. The blood samples were taken at 1, 2, 3, 4, 6, and 8 h, and urine was collected 0–4 h, 4–8 h, 8–12 h and 12–24 h after ingestion of disopyramide.

Phenytoin study

Two healthy volunteers, a female (37 years, 64 kg) and a male (35 years, 92 kg), received phenytoin treatment for 1 week (300 and 400 mg daily, respectively). Disopyramide was administered as a single dose, 300 mg to the former and 400 mg to the latter, before starting phenytoin treatment, after 1 week's treatment, and 1 and 2 weeks after cessation of treatment. Blood and urine samples were collected like those in the rifampicin study, except after cessation of treatment 24 h urine samples only were collected. A third volunteer, aged 20 years, who had epilepsy treated with phenytoin for 7 years, got disopyramide 400 mg once. His blood samples were collected at 15, 30, 45, 60, 90 min, and 2, 3, 4, 6, 8, 12, 24 and 30 h, and urine 0–4 h, 4–6 h, 6–8 h, 8–12 h, 12–24 h and 24–30 h after disopyramide dosage.

Blood samples (before and 2 h after a disopyramide dose), and 24 h urine samples were collected also from two patients receiving combined therapy with phenytoin and disopyramide.

Disopyramide study

The 0 and 2 h blood samples and 24 h urine samples were collected from 22 patients having received oral disopyramide therapy from one to several weeks with doses of 400, 600 or 800 mg daily. Twenty-four hour urine samples on the first day and after 1 week of disopyramide treatment were collected from ten patients and seven healthy volunteers.

Analytical procedures

Plasma samples were stored frozen, and assayed for disopyramide and MND by a gas-chromatographic method described elsewhere (Aitio, 1979). Urine samples (also stored frozen until assayed) were diluted 1:10–1:100 as appropriate. The drugs were extracted from diluted urine after alkalinization in 2 × 3 ml chloroform. Otherwise the procedure was similar to that used for plasma.

Results

Rifampicin study

Six patients got a disopyramide dose of 300 mg (mean 3.95 mg/kg), and six others 200 mg (mean 3.2 mg/kg). One patient was excluded because she already before rifampicin treatment had an unexpectedly fast metabolism of disopyramide (the ratio of MND/disopyramide in the 24 h urine was 2.9 before rifampicin treatment increasing to 4.6 after treatment). She had used phenazone (antipyrine) daily for chronic headache.

The plasma levels of disopyramide decreased and those of MND increased distinctly during rifampicin treatment (Figure 1). The effect of rifampicin treatment on the pharmacokinetic parameters of disopyramide and mono-*N*-dealkyldisopyramide can be seen in Table 1. The elimination half-life of disopyramide shortened almost to a half ($P < 0.001$), the AUC of disopyramide decreased to less than a half ($P < 0.001$), and that of MND almost doubled ($P < 0.001$). The renal clearance (0–8 h) of disopyramide decreased significantly, while an insignificant increase was seen in the renal clearance of MND. The amount of unchanged disopyramide (% of dose) excreted in the 24 h urine fell to a fourth, and that of MND rose to 1.6-fold. The change of the ratio of MND/DIS in 24 h urine was 6.9-fold.

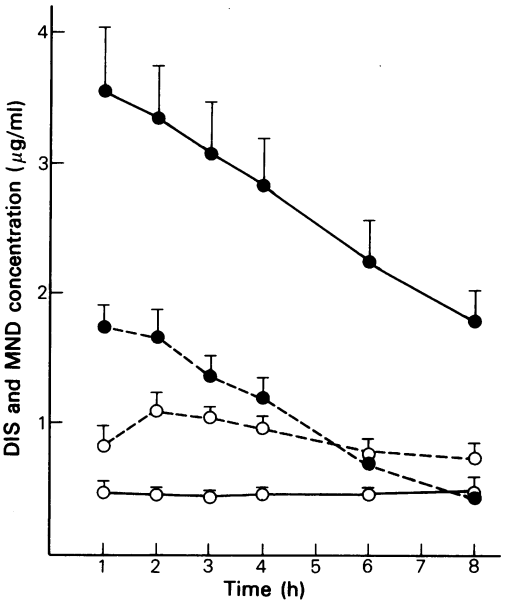

Figure 1 Effect of rifampicin treatment on the plasma levels of disopyramide (DIS) and mono-*N*-dealkyldisopyramide (MND) after a single disopyramide dose (n = 11). ●—● DIS before, ○—○ MND before, ●- -● DIS after, ○- -○ MND after 2 weeks of rifampicin therapy. Means ± s.e. mean have been indicated.

The change in the urinary excretion of disopyramide and mono-*N*-dealkyldisopyramide, and in the ratio MND/DIS in the urine of separate subjects is depicted in Figures 2 and 3.

Table 1 The effect of 2 weeks' rifampicin treatment on the pharmacokinetic parameters of disopyramide and mono-*N*-dealkyldisopyramide. Means ± s.d. are indicated, $n = 11$.

	Before treatment	*During treatment*	*Significance*
Disopyramide			
AUC ($\mu g\ ml^{-1}\ h$)	20.3 ± 8.90	8.22 ± 3.25	***
$T_{½}$ el(h)	5.86 ± 1.65	3.25 ± 0.65	***
Renal clearance 0–8 h (ml/min)	55.2 ± 12.6	40.8 ± 19.6	**
X_{u24} (% of dose)	36.2 ± 5.5	8.5 ± 3.1	***
Mono-N-dealkyldisopyramide			
AUC ($\mu g\ ml^{-1}\ h$)	3.53 ± 1.48	6.77 ± 2.26	***
Renal clearance 0–8 h (ml/min)	133.4 ± 54.3	145.6 ± 76.6	NS
X_{u24} (% of dose)	19.3 ± 6.7	30.6 ± 12.9	**
The ratio of mono-N-dealkyldisopyramide/disopyramide in 24 h urine			
MND/DIS	0.562 ± 0.255	3.84 ± 1.62	***

The statistical significances before and after treatment are calculated with the Student's *t*-test for paired data (*** = $P < 0.001$, ** = $P < 0.01$, NS = nonsignificant).
$T_{½}$ el = Elimination half-life
AUC = Area under the plasma level-time curve
X_{u24} = Amount excreted in urine within 24 h

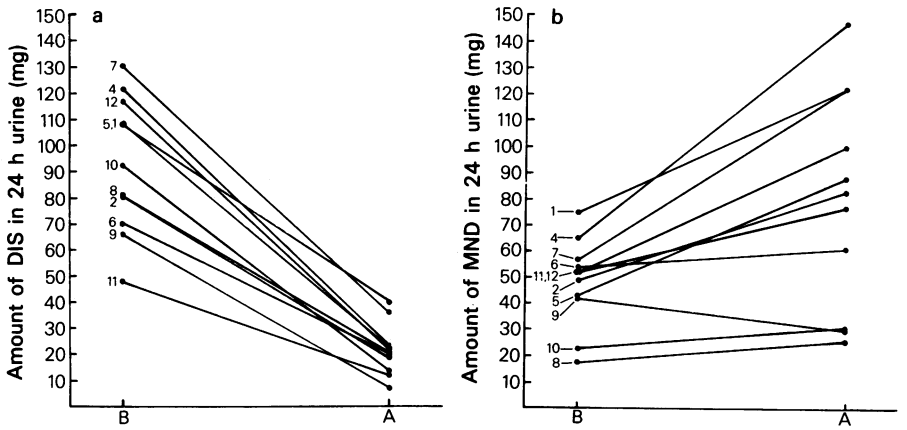

Figure 2 Effect of rifampicin treatment on the urinary excretions of disopyramide (DIS) (a) and mono-*N*-dealkyldisopyramide (MND) (b). B = before, A = after 2 weeks of rifampicin therapy.

Phenytoin study

The data of three volunteers are presented in Tables 2 and 3. In a study on disopyramide pharmacokinetics (Aitio *et al.*, submitted for publication) in healthy volunteers, an epileptic with continuous phenytoin therapy was by oversight included. His pharmacokinetic parameters are compared with those of the others in the same study ($n = 9$). Phenytoin treatment caused similar effects on the metabolism of disopyramide as rifampicin. The effect subsided in 2 weeks (Table 2). The plasma levels and urinary excretion

Table 2 Effect of 1 week's phenytoin treatment on the pharmacokinetic parameters of disopyramide (DIS) and mono-*N*-dealkyldisopyramide (MND) in two healthy volunteers.

	Before treatment Subject		*During treatment* Subject	
	1	*2*	*1*	*2*
Disopyramide				
AUC (μg ml^{-1} h)	22.9	21.3	14.1	15.0
$T_{½}$ el (h)	8.2	6.4	2.5	5.3
Renal clearance 0–8 h (ml/min)	80.0	103	55.4	82.9
X_{u24} (% of dose)	46.5	47.2	18.6	24.0
Mono-N-dealkyldisopyramide				
AUC (μg ml^{-1} h)	3.8	3.8	9.5	6.7
Renal clearance 0–8 h (ml/min)	140	193	159	185
X_{u24} (% of dose)	21.4	24.9	45.8	38.7

MND/DIS in 24 h urine

	Before treatment	*During treatment*	*1 week after treatment*	*2 weeks after treatment*
Subject 1	0.46	2.5	1.5	0.45
Subject 2	0.53	1.6	0.96	0.67

AUC = Area under the plasma level-time curve
$T_{½}$ el = Elimination half-life
X_{u24} = Amount excreted in urine within 24 h

of disopyramide and MND in two patients with combined phenytoin and disopyramide therapy are seen in Table 4. The ratio MND/DIS is high in the plasma and urine. The change caused by phenytoin therapy is seen in the patient H.H.

Disopyramide study

The plasma levels and the ratios of MND to disopyramide in the plasma in 0 h and 2 h samples and in the 24 h urine in 19 patients with long term disopyramide therapy with daily doses of >8 mg/kg, 8 – 6.5 mg/kg and <6.5 mg/kg (400–800 mg daily) of disopyramide are seen in Table 5. Out of 22 patients three with a serum creatinine level above 160 μmol/l were excluded. There were no significant differences between the three groups with regard to the age, serum creatinine level and the ratio of MND to disopyramide renal clearance of the patients. The difference in 2 h plasma levels of MND and in the ratios of MND/DIS of 2 h plasma and 24 h urine was almost significant ($P < 0.05$) between the highest (I) and the

Table 3 Pharmacokinetics of disopyramide (DIS) and mono-*N*-dealkyldisopyramide (MND) in an otherwise healthy epileptic under continuous (7 years) therapy with phenytoin compared with those of healthy volunteers. Data based on measurements during 30 h after the drug dose.

	Controls	*Epileptic*
Disopyramide		
AUC (μg ml^{-1} h)	57.6 ± 10.3*	24.2
$T_{½}$ el (h)	8.6 ± 1.4	4.0
Renal clearance (ml/min)	69.4 ± 11.6	19.8
X_{u30} (% of dose)	52.5 ± 4.3	14.3
Mono-N-dealkyldisopyramide		
AUC (μg ml^{-1} h)	12.2 ± 4.9	22.4
Renal clearance (ml/min)	143 ± 58	129
X_{u30} (% of dose)	23.6 ± 4.6	43.3
MND/DIS in urine	0.46 ± 0.11	3.0

* Means ± s.d. from nine persons are indicated
AUC = Area under the plasma level-time curve
$T_{½}$ el = Elimination half-life
X_{u30} = Amount excreted in urine within 30 h

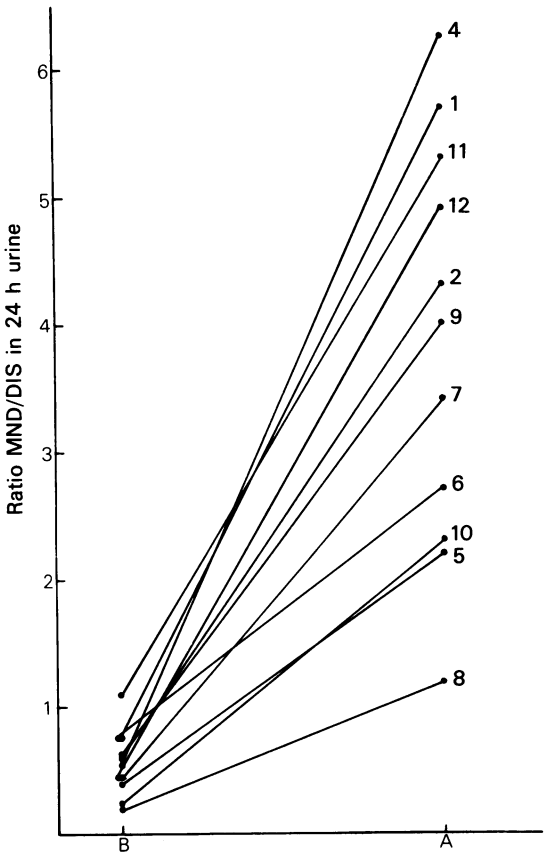

Figure 3 Effect of rifampicin treatment on the MND/DIS ratio in urine. B = before, A = after 2 weeks of rifampicin therapy.

lowest (III) dosage group; all other differences were statistically nonsignificant.

The MND/DIS ratio in 24 h urine after 1 week's treatment was elevated 1.8-fold in 10 patients, and 1.9-fold in seven volunteers (Table 6).

Discussion

The accelerating effect on the metabolism of disopyramide caused by rifampicin and phenytoin was beyond controversy. The plasma levels and AUC of disopyramide decreased, those of mono-*N*-dealkyldisopyramide increased, and the ratio MND/DIS in 24 h urine increased distinctly in all patients studied. During rifampicin treatment the mean plasma levels of disopyramide did not reach the assumed therapeutic range 2–5 μg/ml (Koch-Weser, 1979) (Figure 1), though the disopyramide doses used were loading doses generally recommended.

The renal clearance of disopyramide declined after rifampicin and phenytoin treatment. This agrees with the results of Cunningham, Shen, Shudo & Azarnoff (1977) who reported a decrease of the renal clearance of disopyramide with time after a single dose, in parallel with decreasing total disopyramide plasma levels. They could not find a completely satisfactory explanation for this. In clinical practice disopyramide and rifampicin only occasionally occur together, whereas phenytoin is used also as an antiarrhythmic agent not infrequently. The data of two patients show the effect of phenytoin in clinical practice: in the patient P.M. the plasma disopyramide levels are mainly below the recommended therapeutic range despite the large disopyramide dose used, and also the patient H.H. needed a dose of 800 mg to exceed the lower limit of the therapeutic level.

We tried to elucidate the problematic question of the inducing effect of disopyramide itself in a variety of ways. In the patients with various doses of disopyramide almost significant differences were seen

Table 4 Plasma levels before (0 h) and 2 h after (2 h) disopyramide dose and urinary excretion of disopyramide (DIS) and mono-N-dealkyldisopyramide (MND) in two patients with combined phenytoin (DPH) and disopyramide therapy.

Patient and daily dose of DIS (mg)		*Drug plasma levels during DPH therapy (μg/ml)*		*Urinary excretion of drugs (mg/day)*	
		0 h	*2 h*	*Before DPH*	*During DPH*
H.H.	DIS	2.3	2.9	262	118
600–800	MND	1.7	1.7	110	299
P.M.	DIS	0.7	1.6	—	—
600	MND	1.2	1.3	—	—
P.M.	DIS	1.6	2.5	—	145
800	MND	1.9	2.0	—	384

Table 5 The plasma levels of disopyramide and mono-*N*-dealkyldisopyramide and the ratios of mono-*N*-dealkyldisopyramide to disopyramide (MND/DIS) in the plasma and in 24 h urine in patients with long term disopyramide therapy with various doses (mean ± s.d.).

	Group I	*Group II*	*Group III*
Daily dose	>8 mg/kg	8–6.5 mg/kg	<6.5 mg/kg
n	5–6	4–5	7–8
Age years	59.2 ± 10.6	54.4 ± 16.2	64.1 ± 5.1
Drug plasma level (μg/ml)			
DIS 0 h	2.4 ± 1.8	2.5 ± 0.6	3.2 ± 1.1
DIS 2 h	4.2 ± 2.4	3.3 ± 1.1	3.7 ± 1.3
MND 0 h	1.7 ± 1.2	1.0 ± 0.5	1.2 ± 0.5
MND 2 h	2.4 ± 1.0	1.1 ± 0.5	1.1 ± 0.5*
Ratio MND/DIS			
plasma 0 h	0.87 ± 0.42	0.40 ± 0.15	0.36 ± 0.10
plasma 2 h	0.67 ± 0.30	0.37 ± 0.19	0.28 ± 0.09*
24 h urine	0.96 ± 0.44	0.56 ± 0.14	0.46 ± 0.16*
Serum creatinine (μmol/l)	91.0 ± 24.3	100.4 ± 21.9	113.3 ± 21.8
MND clearance/ DIS clearance (renal)	1.31 ± 0.27	1.59 ± 0.62	1.67 ± 0.98

* Statistically significantly ($P < 0.05$, Student's *t*-test) different from the value in group I. No other differences were significant.

Table 6 The ratios of mono-*N*-dealkyldisopyramide (MND) to disopyramide (DIS) in the 24 h urine on the first disopyramide treatment day and after 1 week's treatment in ten patients and seven healthy volunteers (means ± s.d.). The statistical significance is calculated with the Wilcoxon test for paired data (** = $P < 0.01$, * = $P < 0.05$).

	MND/DIS_{urine}		
	First day		*1 week's treatment*
Patients $n = 10$	0.60 ± 0.31	**	1.13 ± 0.99
Volunteers $n = 7$	0.44 ± 0.11	*	0.80 ± 0.26

only between the highest and lowest dosage group. In two patients in the group with a disopyramide dose above 8 mg/kg the MND/DIS ratios in the urine were 1.7 and 1.3, and thus well above those generally seen, but rather far from those seen during rifampicin treatment. Both of them had used disopyramide for several months, and no data were available from the starting point of the treatment. The MND/DIS ratio showed a rising tendency from the lowest to the highest dosage group, though all differences were not significant.

There was a significant difference in the urinary MND/DIS ratios between the first and seventh treatment days both in patients and in volunteers. However, the elimination half life of MND is longer than that of disopyramide (Hinderling & Garrett, 1976). So the situation is not pharmacokinetically exactly similar on the first day and after 1 week's treatment. The first day was chosen to be sure to avoid early enzyme induction. The change is anyway much smaller than that caused by the strong inducers. There was one patient in this group, in whom the change of the urinary MND/DIS ratio was 4.4-fold (MND/DIS in urine after one week's treatment 3.6). It was confirmed that she was not administered any known enzyme inducing drugs simultaneously. She had a very severe cardiac failure, and her serum creatinine was normal. Her MND/DIS ratio is at the level generally seen after treatment with strong inducers, and the 4.4-fold change can hardly be explained from the difference of pharmacokinetics of disopyramide and MND on the first and seventh treatment day.

The only study about enzyme induction by disopyramide in man so far is that by Rycroft & Daniel (1976). They used D-glucaric acid as an indicator of induction, and did not see any effect attributable to disopyramide. There is, however, not always any correlation between the production of D-glucaric acid and enzyme induction (Marselos, Törrönen & Aitio, 1978; Freundt, 1979). Chronic disopyramide therapy lasting over 10 days caused a slight decrease in the disopyramide plasma levels in a patient series (Aitio, 1981). In the rat a strong enzyme inducer, phenobarbitone, caused an about four-fold increase in the metabolism of disopyramide, whereas disopyramide proved to be a weak inducer of its own metabolism (Aitio & Aitio, 1979). Thus it seems probable that disopyramide can induce its own metabolism, though it is probably clinically unimportant.

Pharmacokinetically the effect of strong inducers was significant. The accelerated metabolism produces more MND. The protein binding of MND in man is about one fourth of that of disopyramide (Aitio, 1981). More of MND thus is in free, active form. MND has some anti-arrhythmic activity (Grant, Marshall & Ankier, 1978). Thus an increased rate of metabolism of DIS cannot be equated with a shorter duration of response.

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