ENHANCED METABOLISM AND DIMINISHED EFFICACY OF DISOPYRAMIDE BY ENZYME INDUCTION?

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- 1 Monitoring plasma levels of mono-N-dealkyldisopyramide (MND), the most important metabolite of disopyramide, has been considered unnecessary.
- 2 We measured plasma levels of both disopyramide and MND in 64 consecutive patients receiving long term oral therapy with disopyramide.
- 3 Six patients were found with high plasma levels of MND, and simultaneously low levels of disopyramide.
- 4 Three of these patients were taking simultaneously phenytoin. The other three had a relatively high dose of disopyramide with regard to their renal function. One patient had terminal uremia, three had less severe renal dysfunction.
- 5 The underlying mechanism and clinical significance of the findings are discussed.

Introduction

Disopyramide, (DIS, 4-diisopropylamine-2-phenyl-2-(2-pyridyl)-butyramide) is a new drug that is used in the treatment of cardiac arrhythmias of both atrial and ventricular origin. Its clinical efficacy has been proved in many clinical studies. Reports on the correlation between clinical response and the concentration of the drug in the blood are few, the likely desirable therapeutic range is assumed to be about 3–5 µg/ml plasma (Heel, Brogden, Speight & Avery, 1978). The dose recommended by the manufacturer is 300 to 800 mg daily in adults; in most patients an adequate response is achieved by 100 mg six-hourly.

About 50 to 60% of an administered dose of disopyramide is excreted unchanged, mainly in the urine. The major metabolic pathway of disopyramide in man is N-dealkylation, yielding mono-N-dealkyldisopyramide (MND) that constitutes approximately 25% of the dose, and is also excreted in the urine (Karim, 1975). In two animal studies, MND had antiarrhythmic activity (Baines, Davies, Kellet & Munt 1976; Grant, Marshall & Anker 1978). Its anticholinergic activity was higher than that of disopyramide (Baines *et al.*, 1976). The purpose of the present study was to investigate the value of measuring both disopyramide and MND plasma levels in patients receiving long term oral therapy with disopyramide.

Methods

The plasma levels of disopyramide and mono-N-dealkyldisopyramide were measured in all patients receiving long term oral therapy with disopyramide in the Department of Medicine, University Hospital of Turku, Finland, from January to November, 1978. The blood samples were collected at steady state (the therapy had lasted for more than 2 days), immediately before (0 h), and 2 h after the dose of the drug. The clinicians in charge adjusted the dosage of disopyramide based on the clinical condition of the patient, without knowledge of the drug plasma levels.

Disopyramide and MND were extracted from alkaline plasma with diethylether, back-extracted to weak acid, reextracted again after alkalization into chloroform and quantitated with gas chromatography, after acetylation of MND. The details of the method have been published (Aitio, 1979).

Results

In all, 174 plasma samples from 64 patients were analyzed. The mean trough (0 h) level of disopyramide was 3.16 (s.d. 1.13, range 1.4–6.8) µg/ml, and that of MND 0.93 (s.d. 0.54, range 0–2.8) µg/ml, and the mean peak (2 h) levels were 4.01 (s.d.

Table 1 Patient details and plasma levels of disopyramide and the metabolite

<i>Patient</i>	<i>Age (years) sex</i>	<i>Duration of DIS therapy before sampling</i>	<i>Simultaneous enzyme inducing drugs</i>	<i>Dose of DIS (mg) in sampling time</i>	<i>Serum creati- nine level (μmol/l)</i>	<i>Plasma levels DIS (μg/ml)</i> <i>MND (μg/ml)</i>		
1	54M	1 month	none known	600	1400	0	1.7	5.0
						2 h	3.3	5.6
		2 months	none known	300	1500	0	1.9	3.1
						2 h	2.4	3.0
		3 months	none known	100 every other day	2000	0	0.3	0.8
						2 h	0.7	1.0
2	68F	some days	DPH	400	175	14 h	0.7	1.3
						0	0.9	2.0
		4 months	DPH	600	215	2 h	2.2	2.9
					—102	0	2.5	3.1
		5½ months	DPH	400	133	2 h	3.3	3.9
					tachycardia	0	0.6	1.5
		5½ months	DPH	400	129	2 h	0.8	2.0
					sinus rhythm	0	1.2	2.1
3	73M	2 months	none known	400 (—300)	425	2 h	1.1	2.1
						0	2.7	2.3
4	50M	over ½ year	DPH once	800	140	2 h	6.3	3.1
						0	2.6	2.7
		over ½ year	none known	800	134	2 h	3.3	3.1
						0	4.0	2.5
5	58M	8 months	DPH	1200	82	2 h	4.0	2.5
6	82F	4 days	DPH	600	77	0	3.7	3.1
						2 h	4.0	3.4
						0	2.9	3.3
						2 h	2.5	2.6

DIS=disopyramide DPH=phenytoin 0: sample before next dose
MND=mono-N-dealkylated disopyramide 2h: sample 2 h after dose

Conversion factor for creatinine: Multiply the given value by 0.0113.

1.30, range 1.2–8.3), and 1.09 (s.d. 0.58, range 0–2.8) $\mu\text{g/ml}$, respectively. Six patients were found who had an unusually high plasma level of the metabolite and simultaneously a low level of the parent drug. In order to reveal the cause of this phenomenon, these six patients were further studied. The 26 plasma concentrations determined in these six patients were not included in the average values given above. Patient details and the drug plasma levels have been presented in Table 1.

Patient 1 had hypertension for several years, myocardial infarctions twice, and progressively deteriorating renal function. He had premature ventricular beats unresponsive to β -adrenoceptor blockers, quinidine and procainamide. Disopyramide therapy was introduced with a dose of 200–300 mg daily. Because of unresponsiveness, the dose was increased to 600 mg daily. However, because the renal function progressively deteriorated, the dose of disopyramide was reduced to 300 mg daily, and further to 100 mg every other day. Despite of disopyramide therapy, he had continuously attacks of tachycardia.

Patient 2 had cardiac arrhythmias for several years. After a myocardial infarction she had various sorts of serious arrhythmias, unresponsive to lignocaine, procainamide, practolol and quinidine. Phenytoin was introduced and the patient had taken it for about 7 months when disopyramide (400 mg daily) was started, without effect, however. She received phenytoin combined with disopyramide or various other anti-arrhythmic drugs and repeatedly suffered from arrhythmic attacks. The patient had mild renal dysfunction: serum creatinine levels varied between 215 and 102 $\mu\text{mol/l}$ (2.4–1.2 mg/100 ml).

Patient 3 had chronic nephropathy with serum creatinine level of about 400 $\mu\text{mol/l}$ (4.5 mg/100 ml). Disopyramide therapy had some effect on his cardiac arrhythmias.

Patient 4 had myocardial infarction, cardiac decompensation and cardiac arrhythmias. He had taken disopyramide with favourable effect for several months. After repeated episodes of ventricular fibrillation, the dose of disopyramide was increased

to 800 mg daily. At this time he also received phenytoin 250 mg intravenously once. Disopyramide therapy combined with ajmalin and pindolol continues with reasonably good effect.

Patient 5 had cardiac decompensation and arrhythmias. After several episodes of ventricular fibrillation, disopyramide was introduced, first 400, then 800, and 1200 mg daily. At the same time also phenytoin therapy was started. The combined therapy with disopyramide (1200 mg daily) and phenytoin 300 mg daily continues with favourable effect. However, attempts to reduce the dose of disopyramide resulted in extra beats.

Patient 6 had multiple ventricular premature beats and first degree heart block in ECG. The treatment was first started with phenytoin that the patient received for 7 days. Because of a therapeutic failure, phenytoin was replaced by disopyramide, first 400, then 600 and 800 mg daily. No therapeutic effect was seen.

Discussion

There is no information available on the levels of mono-N-dealkyldisopyramide in long term therapy before this report. After a single therapeutic dose of disopyramide (3 mg/kg), serum concentrations of MND are generally below 0.4 µg/ml (Hutsell & Stachelski 1975). In our patients with long term disopyramide therapy, the MND concentrations were about 1 µg/ml.

The six patients described here were clearly different from the other 58 patients: they had an unexpectedly high plasma level of mono-N-dealkyldisopyramide, while the plasma level of disopyramide was low. Four of these patients had obvious renal dysfunction. Both disopyramide and MND are mainly excreted in the urine (Karim, 1975), and the half-life of disopyramide is prolonged in significant renal impairment (Whiting & Elliot, 1977). The urinary excretion rate of MND is higher than that of disopyramide (Karim, 1975; Hinderling & Garrett, 1976). In the present patients, however, the level of MND was increased while that of disopyramide was not. Urinary excretion rate of disopyramide, and MND, are independent of urinary pH, and urine flow rate (Hinderling & Garrett, 1976); changes in these parameters often seen in renal failure, therefore do not explain the relatively high concentration of MND in these patients. The concentration of p-hydroxydiphenylhydantoin (p-HDPH), the major metabolite of phenytoin (DPH), in plasma, is high in patients with renal failure, and the rate of metabolism of DPH is increased (Letteri, Mellk, Louis, Kutt, Durante &

Glazko, 1971). These findings have been explained as follows: p-HDPH, which is retained in the body, competes with DPH for plasma protein binding sites. Therefore, more of DPH is free, which in turn leads to enhanced metabolic rate of DPH (Letteri *et al.*, 1971). It is, however, unlikely that a similar mechanism could be operative in case of disopyramide and MND: The protein binding of disopyramide is 5 to 65% only, and for competition for binding sites to be metabolically significant, the binding has to exceed 70–80% (Werdinius, 1968). In addition, in contrast to DPH, the half life of disopyramide is increased, not decreased, in renal failure (Whiting & Elliot, 1977).

Three of our patients were simultaneously given phenytoin, a well-known inducer of the hepatic drug metabolizing enzymes. The metabolism of disopyramide is markedly enhanced by phenobarbital in rats (Aitio & Aitio, 1979). We also had a patient, a 58 year old man, in whom phenytoin therapy 300 mg daily was introduced during simultaneous treatment with disopyramide (400 mg daily). Before starting phenytoin therapy the concentrations of disopyramide were 4.6 and 6.7, and those of MND 0.6 and 0.8 µg/ml before and 2 h after the drug administration, respectively. After 1 week of the combined therapy, the concentrations of disopyramide were 3.7 and 5.0, and those of MND 1.3 and 1.4 µg/ml, respectively. So it seems that phenytoin caused a decrease in the concentration of disopyramide, and an increase in the concentration of MND. In this patient, who had normal renal function, no accumulation of either of the drugs was seen, however. Simultaneous therapy with DPH and disopyramide is not unusual. Should enzyme induction occur, it would lead to diminished concentrations of disopyramide with consequent therapeutic inefficiency. At least in patient 2 the plasma levels of disopyramide were below the therapeutic range. On the other hand, stopping phenytoin therapy would lead to increased, maybe toxic levels of disopyramide.

Two of our patients were not taking any known enzyme inducing drugs, and one got DPH only once. None of them was, as far as we know, an alcoholic. We do not know their smoking habits, or occupational chemical exposures, all of which can modify drug metabolizing enzyme activities (Gibaldi, 1977).

Disopyramide weakly stimulates its own metabolism in the rat (Aitio & Aitio, 1979). In healthy humans, disopyramide treatment (400 mg daily) did not increase the urinary excretion of D-glucaric acid (Rycroft & Daniel, 1976). However, D-glucaric acid excretion does not respond to all inducing chemicals (Marselos, Törrönen & Aitio, 1978). In our patients the dose of disopyramide was fairly high in relation to their impaired renal function,

especially so in patient one. Although disopyramide might not stimulate enzyme activities at normal dosage, it might do so when administered in high doses for extended periods of time.

In two animal studies, MND was only slightly less active as an anti-arrhythmic than disopyramide (Baines *et al.*, 1976, Grant *et al.*, 1978). According to Grant *et al.* (1978), MND has a positive inotropic effect on isolated cardiac muscle, in contrast to disopyramide. So accumulation of MND might help counteract the direct depressant effect of the parent drug. In animal studies, the anticholinergic activity of MND was stronger than that of disopyramide (Baines *et al.*, 1976); so MND would tend to increase the adverse side effects of disopyramide, that are mainly anticholinergic.

The monitoring of the levels of both disopyramide and its major metabolite, MND, revealed to us an interesting, thus far unknown, finding of the likely enhancement of the metabolism of disopyramide by enzyme inducing drugs in man. If verified, this certainly has clinical importance. We suggest the measuring of both disopyramide and MND levels when there is a discrepancy between the blood level of disopyramide and the given dose, when treating a patient simultaneously with an enzyme inducing drug, and when the renal function is impaired.

We gratefully acknowledge Turku University Foundation and Lääke-Medipolar Research Foundation.

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(Received May 22, 1979)