Br. J. clin. Pharmac. (1985), **20**, 453–458

The influence of age and smoking on the elimination of disopyramide

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1 The influences of smoking and age on the elimination kinetics of disopyramide were studied in 27 subjects. Total elimination clearance of disopyramide was measured after an infusion to steady state.

2 The total elimination clearance was significantly ($P < 0.05$) decreased in elderly non-smoking patients compared with young non-smoking subjects (1.54 ± 0.33 *vs* 2.12 ± 0.67 ml kg^{-1} min^{-1}) (mean ± s.d.).

3 Smoking more than 20 cigarettes per day significantly ($P < 0.05$) increased total elimination clearance in elderly (2.02 ± 0.35 *vs* 1.54 ± 0.33 ml kg^{-1} min^{-1}), while no significant induction by tobacco was observed in young healthy persons.

4 Serum concentrations of α_1-acid glycoprotein, the major binding protein of disopyramide, were significantly higher ($P < 0.001$) in the elderly patients. However, the volume of distribution (V) was significantly ($P < 0.001$) greater in the elderly patients (2.44 ± 0.64 *vs* 1.16 ± 0.15 1 kg^{-1}). Steady-state serum concentrations of the free drug were significantly ($P < 0.01$) lower in the young volunteers (0.75 ± 0.13 μg ml^{-1}) than in the elderly (0.90 ± 0.10 μg ml^{-1}).

5 The half-life of disopyramide was significantly shorter ($P < 0.01$) in the young volunteers than in the elderly patients.

6 No difference was observed in the relationship between the serum concentration of disopyramide and its main dealkylated metabolite in the groups studied.

7 The results indicate that it might be advisable to reduce the dosage of disopyramide by approximately 30% in elderly non-smokers compared with young subjects.

Keywords disopyramide age smoking pharmacokinetics

Introduction

Advanced age affects the elimination of many drugs. The age dependent decrease in renal function reduces the elimination of drugs excreted mainly unchanged. The elimination of drugs predominantly metabolized is often affected by increasing age (Greenblatt *et al.*, 1982; Massoud, 1984), due to either reduced hepatic blood flow or decreased activity of the microsomal enzyme system. The age dependent decrease in drug metabolism primarily affects compounds such as antipyrine (Bach *et al.*, 1981) and chlordiazepoxide (Roberts *et al.*, 1978) which undergo oxidation. In contrast, phase 2 reactions such as glucuronidation and acetylation seem to be undisturbed by ageing (Massoud, 1984). The influence of age on drug metabolism

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has to be separated from the effect of environmental factors such as cigarette smoking and ethanol intake which can also change the elimination of some drugs (Vestal & Wood, 1980).

Disopyramide is an antiarrhythmic drug excreted to an extent of 50% by the kidneys while the rest undergoes hepatic metabolism primarily to an *N*-dealkylated metabolite (Hinderling & Garrett, 1976). As it is likely to be used in elderly patients with arrhythmias of both supraventricular and ventricular origin, it is mandatory to study its kinetics in such a population.

The aim of the present study was to measure the elimination clearance of disopyramide in young subjects and elderly patients in order to elucidate the influence of age and smoking habits on the total elimination kinetics of disopyramide. Furthermore, we wished to study the serum concentration of α_1-acid glycoprotein in young and elderly subjects since this is the major binding protein for disopyramide. A change in protein binding might alter the free fraction of disopyramide and thus its free concentration, which is probably the parameter determining its pharmacological activity (Huang & Øie, 1982; Lima *et al.*, 1981). An altered protein binding might also change the elimination kinetics of disopyramide.

Methods

The study included 27 persons: twelve were young healthy volunteers, while 15 were elderly patients with ischaemic heart disease. The age of the younger subjects varied from 27–36 years with a mean value of 30.1 years. The mean age of the elderly was 69.0 years with a range of 61–85 years. The weight of the younger subjects varied from 58–93 kg with a mean value of 68.2 kg, while the weight of the elderly ranged from 44–85 kg with a mean value of 68.1 kg. The height varied from 164–190 cm (mean 176) and 155–183 cm (mean 170 cm), respectively. Seven of the young volunteers were females, while twelve in the elderly group were males. Six of the younger subjects and six of the elderly were heavy smokers with a daily consumption of more than 20 cigarettes. All the subjects consumed less than 25 g of ethanol per day. Some of the elderly patients received nitroglycerin and thiazides, but none of the patients was or had been treated with drugs known to interfere with hepatic drug metabolism or blood flow e.g. β-adrenoceptor antagonists.

Informed consent to the study was obtained from all the subjects after careful explanation of the risks and inconveniences to be expected. The protocol was approved by the local ethical committee. All the subjects had normal values of serum creatinine, liver enzymes and coagulation factors.

The clearance of disopyramide was determined after an intravenous bolus injection of 2 mg disopyramide (Norpace, G. D. Searle) per kg body weight followed by a continuous infusion of 18–24 mg h^{-1} according to the dosage schedule suggested by Deano *et al.* (1977). Steady-state serum concentrations were attained after 6–8 h of infusion and the total elimination clearance was calculated by dividing the infusion rate with the steady-state serum concentration taken as an average of three measurements taken at intervals of 1 h. The infusion was then discontinued and the serum concentration of the parent compound and the metabolite were followed in the majority of patients (12 young volunteers and seven elderly patients) during the next 24 h by five or six blood samples taken at intervals of about 4 h.

The elimination half-life was calculated by least squares regression analysis of the log serum concentration with time. The volume of distribution (V) was calculated from the formula:

$$\frac{CL_{total} \times t_{½}}{0.693}$$

The serum concentration of disopyramide and its main dealkylated metabolite were measured by high performance liquid chromatography (Bonde *et al.*, 1985).

Protein binding studies were carried out according to the method described by Norris *et al.* (1982) with a Kontron-Diapack dialysis system equipped with 1.44 ml cells. The membranes were Union Carbide Dialysis tubing (nominal molecular weight cut off 12–14.000 g mol^{-1}) and were pretreated according to the method of Nouravarsani & Cobby (1982). Equilibrium was reached within 6 h at 37°C and 25 rev min^{-1}.

A Beckmann LS-250 instrument was used for liquid scintillation counting and the scintillation liquid was Instagel (Packard). Coloured samples were pretreated with hydrogen peroxide. Plasma (1 ml) obtained from patients during disopyramide treatment was dialysed against 1 ml of 0.05 M phosphate buffer pH 7.30, made isotonic with saline and labelled with 4.259 mCi $mmol^{-1}$[^{14}C]-disopyramide (donated by G. D. Searle). The equilibrium pH was adjusted to approximately 7.40 (37°C). The formulae used to calculate the percentage of bound disopyramide in the samples and the equilibrium concentration of disopyramide are described below.

Percentage of bound disopyramide was calculated from:

$$\% \text{ bound} = \left(1 - \frac{\text{counts in buffer}}{\text{total counts} - \text{counts in buffer}} \right) \times 100$$

Counts from the protein side were not used because of a small but significant change in volume caused by osmosis. Recovery was 95–100%.

$$C_{eq} = \frac{1}{1 + \text{free fraction}} \times (C_{measured} + C_{added} \text{ (with the 14C)}).$$

The data, except values of half-life, were subjected to statistical analysis by Student's unpaired *t*-test with a *P* value less than 0.05 considered as significant. The Mann-Whitney method was used to evaluate the differences between the half-lives as these were considered not to be normally distributed. Due to technical problems protein binding was only determined in nine of the elderly and eleven of the younger subjects.

Results

Table 1 shows total elimination clearance (CL_{total}), volume of distribution (V), half-life ($t_{½}$) and steady state serum concentration of disopyramide (C_{ss}) and its metabolite ($C_{ss,met}$) in the subjects studied. Total clearance of disopyramide was significantly higher in the young volunteers (2.32 ± 0.54 *vs* 1.73 ± 0.41 ml kg^{-1} min^{-1}; $P < 0.02$) and half-life was significantly ($P < 0.01$) shorter in the young volunteers 349 (241–666) *vs* 1078 (550–2472) min, with the figures given as median and range. Volume of distribution (V) was significantly higher in the elderly patients compared to the young volunteers (2.44 ± 0.64 *vs* 1.16 ± 0.15 l kg^{-1}; $P < 0.001$). No significant difference was observed in the relationship between the serum concentrations of the metabolite and the parent compound in the young volunteers compared to the elderly. The steady-state serum concentrations varied from 2.2 to 5.4 μg ml^{-1} with only two subjects having values exceeding 5.0 (5.2 and 5.4 μg ml^{-1}).

Table 2 demonstrates the influence of age and smoking habits on the total elimination clearance of disopyramide in the younger persons compared to the elderly patients. The elimination clearance values of disopyramide were affected by both age and smoking habits. Thus, the mean value of clearance in the young non-smoking group (2.12 ± 0.67 ml kg^{-1} min^{-1}) was significantly ($P < 0.05$) higher than in the elderly non-smoking group (1.54 ± 0.33 ml kg^{-1} min^{-1}). Smoking significantly ($P < 0.05$) increased the total clearance of disopyramide in the elderly persons as the mean value increased from 1.54 ± 0.33 ml kg^{-1} min^{-1} to 2.02 ± 0.35 ml kg^{-1} min^{-1}, while no significant difference was observed between young smokers and non-smokers.

Table 3 shows the free clearance (CL_u) and serum concentrations of α_1-acid glycoprotein in the two groups studied. The free fraction of disopyramide was identical in the two groups. Total and free steady-state serum concentrations of disopyramide were significantly lower in the young volunteers (2.52 ± 0.43 *vs* 3.06 ± 0.36 μg ml^{-1}; $P < 0.01$ and 0.75 ± 0.13 *vs* 0.90 ± 0.10 μg ml^{-1}; $P < 0.01$, respectively). Because of an identical free fraction at steady-state the intrinsic clearance (CL_u) was significantly higher in the young persons (8.21 ± 1.31 *vs* 5.98 ± 0.93 ml kg^{-1} min^{-1}; $P < 0.001$). Serum concentrations of α_1-acid glycoprotein were significantly higher in elderly patients (22.7 ± 4.6 *vs* 15.3 ± 2.0 μmol l^{-1}; $P < 0.001$) than in the younger subjects.

The drug was well tolerated and no adverse reactions were observed.

Discussion

We have demonstrated a significant decrease in the total elimination clearance of disopyramide

Table 1 Kinetic parameters of disopyramide and steady-state serum concentration of its main dealkylated metabolite in young and elderly subjects. All figures are expressed as mean and s.d. except half-life and age which are given as median and range. Six of the young and two of the elderly patients were heavy smokers.

		Young volunteers	*Elderly patients*	*Significance*
Number of patients		12	7	
Mean age and range	(years)	30,1(27–36)	69,0(61–85)	
CL_{total}	(ml kg^{-1} min^{-1})	2.32 ± 0.54	1.73 ± 0.41	$P < 0.02$
V	(l kg^{-1})	1.16 ± 0.15	2.44 ± 0.64	$P < 0.001$
$t_{½}$	(min)	349(241–666)	1078(550–2472)	$P < 0.01$
$C_{ss,\ total}$	(μg ml^{-1})	2.77 ± 0.86	3.97 ± 0.80	$P < 0.01$
$C_{ss,\ met}$	(μg ml^{-1})	0.32 ± 0.19	0.66 ± 0.41	$P > 0.05$

Table 2 Total elimination clearance values of disopyramide in the four groups of subjects studied. The figures are given as (ml kg^{-1} min^{-1}); n indicates the number of subjects in the different groups.

	Young volunteers	*Elderly patients*
Smoking (> 20 cigarettes/day)	2.52 ± 0.39 (n = 6)	2.02 ± 0.35 (n = 6)
No smoking	2.12 ± 0.67 (n = 6)	1.54 ± 0.33 (n = 9)
Significance		
Young smokers *vs* elderly smokers	$P < 0.05$	
Young non-smokers *vs* elderly non-smokers	$P < 0.05$	
Elderly smokers *vs* elderly non-smokers	$P < 0.05$	
Young smokers *vs* young non-smokers	$P > 0.05$	

in elderly patients compared to younger healthy subjects. An age dependent reduction in clearance has been demonstrated for other antiarrhythmics such as procainamide (Reidenberg *et al.*, 1980) and quinidine (Ochs *et al.*, 1978), which like disopyramide are eliminated partly by hepatic metabolism and partly by renal excretion. This age related decrease in total clearance of disopyramide can be explained by the well known age reduction in renal function (Kampmann *et al.*, 1974) as disopyramide is excreted unchanged in the urine to an extent of about 50% (Hinderling & Garrett, 1976).

Like many other basic drugs (Piafsky & Borgå 1977; Piafsky *et al.*, 1978) disopyramide is bound to α_1-acid glycoprotein in plasma (Lima *et al.*, 1981; Bredesen & Kierulf, 1984). α_1-acid glycoprotein is an acute phase reactant of a heterogenous composition (Hansen *et al.* 1984) known to increase non-specifically in response to acute stress including acute myocardial infarction (David *et al.*, 1983). The serum concentration of α_1-acid glycoprotein was lower in the young volunteers than in the elderly. Because of the strong negative correlation between serum concentrations of α_1-acid glycoprotein and the free fraction of disopyramide (Bredesen & Kierluf, 1984), high values of α_1-acid glycoprotein tend to decrease the free fraction, and thus the free concentration of the drug. This decreased free concentration leads to a decrease in its renal excretion (for drugs excreted by glomerular filtration) and for some drugs to delayed hepatic metabolism (Wilkinson & Shand, 1975), thereby resulting in increased total serum concentrations. Due to the dose-dependent protein binding of disopyramide, an increased total concentration results in an increased free fraction. Our results of an unchanged free fraction might represent a balance between these opposite mechanisms. The increased free concentration of disopyramide in the elderly is a result of a decreased clearance and implies that equal doses of disopyramide to young and elderly subjects might give a more pronounced effect with increasing age.

Volume of distribution was increased in the elderly compared to the young volunteers (Table 1). An increased volume of distribution with advancing age has also been demonstrated for other lipid soluble drugs such as lignocaine (Nation & Triggs, 1977) and diazepam (Klotz *et al.*, 1975), and might be a result of an increased amount of adipose tissue in the elderly. This is in accordance with disopyramide being a relatively lipid soluble drug with a chloroform/water partition coefficient of 3.1 (Karim *et al.*, 1978).

In many previous studies concerning the correlation between age and kinetics the results have been confounded by lack of separation of

Table 3 Free clearance (CL_u), free fraction at steady state (f_u), the total and free steady state serum concentration of disopyramide ($C_{ss,total}$ and $C_{ss,u}$, respectively) and serum concentrations of α_1-acid glycoprotein in young and elderly patients. Values are given as mean ± s.d.

	Young volunteers *Mean age 30 (27–36) years*	*Elderly patients* *Mean age 69 (61–85) years*	*Significance*
Number of patients	11	9	
CL_u (ml kg^{-1} min^{-1})	8.21 ± 1.31	5.98 ± 0.93	$P < 0.001$
f_u – (%)	30.0 ± 4.3	30.0 ± 3.8	NS
$C_{ss,total}$ (μg ml^{-1})	2.52 ± 0.43	3.06 ± 0.36	$P < 0.01$
$C_{ss,u}$ (μg ml^{-1})	0.75 ± 0.13	0.90 ± 0.10	$P < 0.01$
α_1-acid glycoprotein (μmol l^{-1})	15.3 ± 2.0	22.7 ± 4.6	$P < 0.001$

age itself from environmental factors such as medication, smoking habits and diet (Jusko, 1978). Our patients all received a normal Danish diet and had a daily consumption of less than 25 g of ethanol. The age dependent reduction in total elimination clearance of disopyramide between the two groups was demonstrated in both smokers and non-smokers. Smoking increased the elimination clearance in both the elderly and young groups, but reached a level of statistical significance only in the elderly. The average increase in clearance in the elderly was 31% (95% confidence limits: 6 to 56%). With regard to the young volunteers the risk of overlooking a difference in clearance values between the two groups, i.e. young non-smokers *vs* young smokers, of 0.40 or 1.0 ml kg^{-1} min^{-1} was 50 and 3%, respectively (type 2 error).

The infusion model used (Deano *et al.*, 1977) resulted in steady-state serum concentrations which in almost all subjects were within the assumed therapeutic range of 2–5 μg ml^{-1} (Niarchos, 1976).

Assuming an age-independent sensitivity to disopyramide, (a fact which has not yet been established for any of the type IA antiarrhythmics), the clinical implication of our findings might be to decrease the intravenous dose of disopyramide by 30% when given to elderly non-smokers.

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(Received 29 January 1985, accepted 28 June 1985)