Br. J. clin. Pharmac (1980), **9**, 21–25

ANTIPYRINE ELIMINATION BY PATIENTS UNDER TREATMENT WITH MONOAMINE OXIDASE INHIBITORS

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1 Antipyrine elimination kinetics have been determined in fifteen patients before and after 4 weeks treatment with monoamine oxidase inhibitors and in five patients after treatment only.

2 Antipyrine elimination was slightly but significantly slowed by 28 days treatment with phenelzine but the degree of slowing was uninfluenced by acetylator phenotype or dosage of phenelzine administered.

3 The findings suggest that at the dosage used phenelzine is a weak inhibitor of hepatic microsomal mixed function oxidase in man and it is concluded that this is likely to provide an important source of drug interaction in some patients.

Introduction

It is well recognized that treatment with monoamine oxidase inhibitors exposes patients to the risk of serious interactions with other drugs and with foodstuffs containing sympathomimetic amines. Some of the interactions appear to be essentially pharmacodynamic in nature and can be explained on the basis of exaggerated responses to exogenous or endogenous biologically active amines. Thus animal experiments indicate that reactions involving pethidine (Rogers & Thornton, 1969) and amphetamine (Simpson, 1978) are probably of this type. It is, however, usually assumed that many other interactions, involving hypnotics, tricyclic antidepressants and other agents, are pharmacokinetic in origin and involve inhibition of hepatic microsomal mixed function oxidase activity. Monoamine oxidase inhibitors influence a wide spectrum of enzyme activity (Pletscher, Gey & Zeller, 1960) and inhibit hexobarbitone oxidation (Laroche & Brodie, 1960) and pethidine N-demethylation (Clark, Thompson & Widdrington, 1972) by animal liver homogenates.

There appears, however, to be no direct evidence of inhibition of hepatic microsomal mixed function oxidase activity in man. The present study was designed to determine the influence of phenelzine on hepatic drug oxidation in man by measurement of antipyrine clearance in psychiatric patients before and after treatment with this drug.

Methods

Patients

Twenty patients of both sexes with anxiety, phobic or depressive neuroses took part in the study. Their informed consent to the procedures involved was obtained and ethical approval for the study was given by St Thomas' Hospital Research Committee and the Joint Ethical Sub-committee of the Hampshire Area Health Authority and the Faculty of Medicine of Southampton University. Most patients had received drug treatments previously. Some of these were discontinued before the study, others were continued throughout. Details of these treatments with the age, sex and body weight of the patients are given in Tables 1 and 2.

Procedures

Fifteen patients had antipyrine elimination kinetics determined before and after 4 weeks treatment with a

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0306–5251/80/010021–5 $01.00

Table 1 Clinical details and antipyrine elimination kinetics in fifteen patients before and after 4 weeks phenelzine administration

Subject	*Sex*	*Age (years)*	*Body weight (kg)*	*Acetylator phenotype*	*Drug treatments (mg/day)*	*Stopped**	*Final phenelzine dosage (mg/day)*	*Antipyrine elimination kinetics*				
								V_d (l)	*K_{el} (h^{-1})*	SE_k	$T_{\frac{1}{2}}$ (*h*)	*Clearance (ml/min)*
1	F	54	57.2	R	dothiepin (150)	9	0	32.4	0.066	0.004	10.6	35
			57.3		thioridazine (150)	9	45	33.3	0.066	0.003	10.5	37
					chlormethiazole (100)	—						
2	F	56	50.0	S	nitrazepam (5–10)	—	0	37.2	0.053	0.001	13.0	33
			46.1				45	32.4	0.036	0.003	19.3	19
3	F	32	44.8	R	diazepam (10)	30	0	25.7	0.082	0.002	8.5	35
			43.8				45	26.6	0.079	0.006	8.8	35
4	F	54	51.3	S	amylobarbitone (200)	14	0	28.6	0.123	0.016	5.6	59
			—		nitrazepam (5)	—	45	30.0	0.057	0.003	12.1	29
5	F	40	44.5	S	amitriptyline (150)	14	0	27.7	0.090	0.003	7.7	42
			43.7		nitrazepam (10)	—	90	28.1	0.042	0.004	16.5	20
6	M	57	—	—	clomipramine (75)	90	0	48.4	0.064	0.001	10.8	52
			—		diazepam (6)	—	30	46.2	0.074	0.001	9.3	57
7	F	45	57.3	R	amitriptyline (75)	21	0	32.5	0.100	0.004	6.9	54
			57.4				45	33.3	0.081	0.006	8.6	45
8	F	51	45.8	S	diazepam (10)	—	0	38.7	0.068	0.012	10.2	44
			42.7				Isocarboxazid 30	31.1	0.080	0.004	8.7	41
9	F	24	53.0	S	amitriptyline (50)	10	0	28.9	0.069	0.003	10.0	33
			53.5		diazepam (10)	—	90	30.3	0.057	0.001	12.2	29
10	F	50	65.0	R	chlorpromazine (50)	—	0	32.3	0.028	0.001	24.3	15
			73.0				90	28.7	0.036	0.001	19.3	17
11	M	37	75.6	S	dichloralphenazone (1300)	—	0	—	0.185	0.013	3.8	—
			75.8				45	—	0.239	0.014	2.9	—
12	F	60	63.0	R	flurazepam (15)	—	0	32.0	0.060	0.009	11.5	32
			62.5				90	32.4	0.041	0.002	16.8	22
13	M	22	68.5	S	propranolol (40)	7	0	35.5	0.098	0.011	7.1	58
			68.2		diazepam (15)	—	45	38.1	0.106	0.008	6.5	67
14	F	52	67.3	S	nitrazepam (10)	—	0	38.3	0.070	0.013	9.9	45
			66.9				90	48.8	0.037	0.004	18.7	30
15	F	25	46.7	S	—		0	21.1	0.055	0.004	12.6	19
			46.7				90	26.5	0.021	0.005	33.6	9

* days before start of investigation
— = continued throughout study

Table 2 Clinical details and antipyrine elimination kinetics in five patients treated with phenelzine

							Phenelzine treatment		*Antipyrine elimination kinetics*				
Subject	*Sex*	*Age (years)*	*Body weight (kg)*	*Acetylator phenotype*	*Drug treatments (mg/day)*	*Stopped**	*Dosage (mg/day)*	*Duration (months)*	V_d (*l*)	K_{el} (h^{-1})	SE_k	$T_{\frac{1}{2}}$ (*h*)	*Clearance (ml/min)*
1	F	64	59.5	R	—		45	12	24.5	0.128	0.010	5.4	52
2	F	58	76.4	—	—		45	1	30.8	0.046	0.001	15.2	23
3	F	43	52.4	R	imipramine (100)	30	45	1	38.1	0.040	0.001	17.4	25
4	F	34	53.0	—	nitrazepam (10)	—	30	9	30.5	0.048	0.002	14.5	24
5	M	21	70.2	—	lorazepam (2)	—	45	12	44.6	0.080	0.005	8.6	60

hydrazine monoamine oxidase inhibitor. All except one of the patients took phenelzine and were involved in a clinical trial of two different dosage regimens of phenelzine (Tyrer *et al.*, 1979). All these patients took 15 mg phenelzine daily for 2 days, increasing to 30 mg daily from 2–7 days. After 7 days treatment the dose was increased to 45 mg or 90 mg daily using a double-blind procedure. One patient received isocarboxazid 30 mg daily. Acetylator phenotype was determined using Schröder's method (1972). Sulphadimidine was used as the test drug in a dose of 10 mg/kg body weight and a urine sample obtained 4–6 h later for phenotyping. Antipyrine elimination kinetics were determined following an oral load (500 or 600 mg), serum samples taken over the succeeding 24 h being assayed for antipyrine by the method of Mendelsohn & Levin (1960).

In five further patients elimination was measured only after periods of treatment with phenelzine ranging from 1 to 12 months, in a dose of 30–45 mg daily.

Assessment

The kinetics of antipyrine elimination were assessed by the method of least squares fit to the data. Treatment effects were measured by paired *t*-tests and the influences of acetylation phenotype and phenelzine dosage by analysis of variance.

Results

The antipyrine elimination kinetic variables of 15 patients tested before and after institution of treatment with monoamine oxidase inhibitors (Group I) are given in Table 1. In Group I the apparent volume of distribution, 0.584 ± 0.032 l/kg, was unchanged by the treatment. Treatment also had no effect on the mean elimination constant ($0.081 \pm 0.010\ h^{-1}$) (mean $\pm$ s.e. mean) nor elimination half-life (10.2 ± 1.2 h), but mean clearance was significantly reduced from 39.7 ± 3.6 ml/min to 32.6 ± 4.3 ml/min (paired $t = 2.442$, $P < 0.05$).

In the further analysis of these data, four patients were excluded for different reasons, *viz.* nos. 4 and 11 for recent or concurrent consumption of microsomal enzyme-inducing drugs, no. 6 because the acetylation phenotype was not determined and no. 8 because she was given isocarboxazid instead of phenelzine as MAO inhibitor. Among the remaining eleven patients, there was a significant but small reduction in both elimination constant from 0.070 ± 0.006 to $0.055 \pm 0.008\ h^{-1}$ ($t = 2.829$, $P < 0.01$) and clearance 36.4 ± 3.9 to 30.0 ± 4.8 ml/min ($t = 2.346$, $P < 0.05$). Analysis of variance indicated that these reductions were uninfluenced either absolutely or proportionally by either acetylator phenotype or phenelzine dosage.

Antipyrine elimination kinetic variables in the five patients treated only after treatment with monoamine oxidase inhibitor (Group II) are given in Table 2. Values for elimination constant, half-life and clearance fell approximately within the ranges of these variables in the Group I patients.

Discussion

On the evidence of these findings, it appears that phenelzine treatment has a small inhibitory effect on antipyrine elimination in man, suggesting that the drug impairs hepatic microsomal mixed function oxidase activity to a small extent. Thus the drug may predispose to drug interactions of a pharmacokinetic type as argued by Clark *et al.* (1972). Based on determination of clearance, the degree of inhibition produced has, however, been found to vary from none to about 53% and in only five of twelve patients did it amount to more than 30%. Based on measurement of elimination half-life, in only one patient (no. 15 in Group I) was the degree of inhibition sufficient to place the individual outside the 95% confidence limits (mean ± 2 s.d.) of normal subjects as defined by Stevenson (1977). As an inhibitor of drug elimination, therefore, phenelzine is not likely to be of serious importance except in occasional patients.

Most of the patients studied here were taking or had recently taken, other drugs. Two had enzyme inducing agents, withdrawal of which could result in slowing of antipyrine elimination. The findings from these patients have therefore been removed from the analysis. Many of the remainder were receiving, or had recently received, other agents, principally antidepressants, phenothiazines and benzodiazepines. Such treatments might have exerted inhibitory effects on drug metabolism, possibly through substrate competition. In such circumstances their withdrawal would have resulted in accelerated antipyrine elimination. In no case, therefore, does the presence or recent withdrawal of a drug appear to vitiate the conclusion drawn above regarding the influence of the monoamine oxidase inhibitor treatment.

We thank Kevin Moreton and Yousef Auckburally for their help in collecting blood samples and the staff of the General Diagnostics Division of Warner-Lambert Ltd, who carried out the acetylator typing.

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(*Received March 15, 1979*)