PHARMACOKINETICS OF MEXILETINE IN RENAL INSUFFICIENCY

D. EL ALLAF¹, L. HENRARD¹, L. CROCHELET¹,
D. DELAPIERRE², J. CARLIER¹ & A. DRESSE²

¹Institut de Médecine, Département de Clinique et de Pathologie médicales, (Professeur H. van Cauwenberge), Secteur de Cardiologie (Professeur J. Carlier), Hôpital de Bavière, 66, Boulevard de la Constitution, B-4020 Liège, and ²Institut de Pathologie, Laboratoire de Pharmacologie (Professeur A. Dresse), B-4000 Sart-Tilman par Liège 1, Belgium.

1 The aim of this study was to evaluate the influence of renal insufficiency on the plasma pharmacokinetics of mexiletine, a new antiarrhythmic agent, in human beings.

2 Mexiletine was administered orally three times daily for 10 days to 15 patients with chronic renal failure (creatinine clearance lower than 30 ml/min) and to 9 subjects with normal renal function.

3 The use of low doses of mexiletine was possible owing to the development of a new fluorescence h.p.l.c. method with a limit of sensitivity lower than 20 ng/ml.

4 Our results clearly indicate that the plasma kinetics of mexiletine are not modified when the renal clearance of creatinine is higher than 10 ml/min.

Introduction

Mexiletine (Mexitil®) is a new ventricular antiarrhythmic agent (Achuff *et al.*, 1975; Campbell *et al.*, 1973, 1975, 1977; Henrard & Carlier, 1980; Talbot *et al.*, 1973, 1976). Plasma therapeutic concentrations are within the range 0.75–2 µg/ml (Campbell *et al.*, 1978a). Side effects increase at plasma levels greater than 2 µg/ml without improvement in the therapeutic efficacy. The purpose of this experiment was to study the influence of chronic renal failure on the pharmacokinetic parameters of orally administered mexiletine.

Methods

Subjects

Subjects were selected from the inpatient population at 'Bavière' University Hospital. Each patient was carefully evaluated and personally examined by one or more of us. The protocol of this study was approved by the local Ethical Committee.

Patients were subdivided into the following non-overlapping groups:

Control group (group I, Table 1) This group was

Table 1 Biological parameters of the control group

Subject	Sex	Age (years)	Body weight (kg)	Plasma urea (mg/100 ml)	Plasma creatinine (mg/100 ml)	Creatinine clearance (ml/min)
1	M	62	70	44	1	80
2	M	77	72	23	0.6	87
3	F	73	56	21	0.8	—
4	M	73	68	30	1	75
5	M	62	65	33	0.9	85
6	M	74	73	38	0.9	117
7	M	51	75	27	0.6	82
8	M	65	78	38	1.1	78
9	M	50	76	29	1	82

made up of nine subjects (8 males and 1 female; the age ranged between 50 and 77 years; the mean age was 65 years). These patients did not have congestive heart failure, poor renal function or impaired liver function.

Poor renal function (group II, Table 2) This group included 15 patients with chronic renal failure (8 males and 7 females; the age ranged between 31 and 73 years; the mean age was 63 years). These patients had histories of intrinsic renal disease and physical and laboratory evidence of progressive azotemia or uraemia. Only males and females having a creatinine clearance lower than 30 ml/min were considered in the experimental group. All patients with hepatic dysfunction, cardiac failure and major electrolyte disturbances were excluded. The following drugs were avoided: barbiturates, antiepileptics, rifampicin (for its induction effects), and other antiarrhythmics. It was necessary to maintain six patients on aluminium hydroxide (Aldrox®) (patients 1, 8, 9, 10, 12 and 13).

The dose of mexiletine given was deliberately chosen below the drug's data sheet recommendations, to produce subtherapeutic blood levels, and so minimize the risk of side effects.

Mexiletine (50 mg) was given orally three times daily (08.00 h, 16.00 h, 24.00 h) for 10 days.

Blood samples (8 ml heparinized blood) were taken:

- before administration of the drug,
- from the 4th to the 10th day (when steady-state level was reached at 07.45 h and 15.45 h),
- from the 11th to the 13th day (at 07.45 h, 15.45 h and 23.45 h).

The pH of the urine was measured shortly after micturition using a pH meter from the 11th to the 13th day.

Method of assay

Mexiletine was extracted twice with 4 ml diethylether after deproteinization of plasma (1 ml) by barium hydroxide (1 ml) and zinc sulphate (1 ml) according to the method described by Somogyi (1945). The two pooled 3 ml aliquots of the organic phase were evaporated to dryness under a nitrogen flow. The residue is dissolved into 0.1 M borate buffer pH 7.9 and the primary amines were combined with fluorecamine (Udenfriend, 1972). The fluorophors were separated at room temperature by a h.p.l.c. Waters Associates system. A C₁₈ reverse phase column was used with following solvent water-methanol (15 : 85 v/v) containing 1-heptane sulphonic acid (final concentration : 0.05 M). The flow rate was 2 ml/min. Mexiletine was quantitatively measured at 390/490 mμ with a fluorometer Waters Associates model 420E. A standard was prepared for each set of samples by adding a known amount of mexiletine to

Table 2 Biological and clinical parameters of patients with chronic renal failure

Patient	Sex	Age (years)	Body weight (kg)	Plasma urea (mg/100 ml)	Plasma creatinine (mg/100 ml)	Creatinine clearance (ml/min)	Serum albumin (g/100 ml)	Underlying disease
1	M	53	65	159	7.9	10	4.5	Diabetic nephropathy
2	F	73	60	94	1.8	14	3.3	Chronic pyelonephritis
3	M	51	63	104	3.3	18	4.0	Chronic interstitial nephritis (phenacetin)
4	M	66	77	112	3.6	29	4.5	Diabetic nephropathy
5	F	62	87	200	3.2	29	4.3	Diabetic nephropathy
6	F	60	75	56	2.5	18	3.6	Renal artery stenosis
7	M	73	61	110	5.1	11	3.6	Chronic pyelonephritis
8	F	54	65	197	7.9	4	3.5	Chronic interstitial nephritis (phenacetin)
9	F	60	70	139	5.5	6	3.9	Nephrosclerosis
10	F	31	60	202	6.7	7.5	3.2	Diabetic nephropathy
11	M	61	65	182	5.3	9	3.9	Chronic pyelonephritis
12	F	72	60	189	5.5	6	4.3	Diabetic nephropathy
13	M	60	59	279	8.3	4	3.4	Chronic pyelonephritis
14	M	57	73	227	5.9	7	3.6	Polycystic kidneys
15	F	66	50	208	7.4	3	4.3	Chronic interstitial nephritis (phenacetin)

blank plasma and carrying the whole procedure through. Mexiletine (20 ng/ml) could be accurately measured by this method. The coefficients of variation were respectively 3.9, 4.8, 4.8, 3.2 and 3.1% at 20, 50, 100, 1000 and 2000 ng/ml.

The principal pharmacokinetic parameters (plasma levels at steady-state and the half-life of elimination) were mathematically calculated after linear regression analysis. Student's *t*-test was used for statistical analysis.

Results (Tables 3, 4 and 5)

The plasma mexiletine half-life was significantly increased in patients with chronic renal failure ($P < 0.05$). The group II was subdivided into two classes: group IIA being those patients with creatinine clearance below 10 ml/min and group IIB being those patients with creatinine clearance between 10 and 30 ml/min. Their results were compared to those of group I. At steady-state, mexiletine plasma concentrations and half-life were not statistically different in group IIB from group I. On the other hand, plasma concentration and half-life were significantly increased in group IIA compared with group I.

Discussion

Following repeated oral administration of 50 mg of mexiletine to the control group, the plasma concentration rose to $0.14 \pm 0.15 \mu\text{g/ml}$ at steady-state and the half-life obtained was 10.35 ± 3.2 h. These values are similar to those found by other authors (Campbell *et al.*, 1978b; Prescott *et al.*, 1977).

Due to an already slow renal elimination of the drug and the large volume in which it is distributed in healthy subjects, only a small accumulation of mexiletine would have been predicted in patients with chronic renal failure (Prescott *et al.*, 1977).

Our study indeed showed that the pharmacokinetic parameters of mexiletine were not

significantly modified in chronic renal failure, when the creatinine clearance was above 10 ml/min. This confirmed our previous results obtained after a single intravenous administration of the drug (Baudinet *et al.*, 1980). However when the creatinine clearance was below 10 ml/min, the plasma concentration at steady-state and the plasma half-life of mexiletine increased to $0.3 \pm 0.15 \mu\text{g/ml}$ ($P < 0.05$) and 15.7 ± 4.9 h ($P < 0.025$). As the pKa of mexiletine is within the critical range of 7.5 to 10.5, its renal clearance is highly dependent on urinary pH (Beckett & Chidomere, 1977; Johnston *et al.*, 1979; Kiddie *et al.*, 1974), being far greater in an acidic pH. The increase in the plasma half-life of mexiletine in group IIA cannot be explained by an alkalinisation of the urine (Table 4). In addition, despite treatment by aluminium hydroxide (Aldrox®) in some patients (patients 1, 8, 9, 10, 12 and 13) urinary pH remained less than or equal to 6.5 in all cases. Furthermore, there is no correlation between values of urine pH and plasma half-life of mexiletine within our pH limits.

Our results are not in agreement with those of Herbinger *et al.* (1978) who concluded that plasma mexiletine levels and half-life were not related to creatinine clearance. They, however, studied only five cases, where four were patients with creatinine clearance below 10 ml/min. The values they published varied greatly from one patient to another and one of the four with creatinine clearance below 10 ml/min did indeed show a rather large value of mexiletine plasma half-life (26.9 h).

In summary, our results showed that the usual dose of mexiletine can be given without any modification to patients with chronic renal failure having a creatinine clearance above 10 ml/min.

However in patients with renal insufficiency having a creatinine clearance below 10 ml/min it is important to follow plasma mexiletine levels in order to adapt the dosage of the drug.

We wish to express our thanks to Professor Prescott who helped us in the design of this protocol and Dr Goossens for his appreciated assistance.

Table 3 Pharmacokinetic parameters of mexiletine in the control group

	Subjects								
	1	2	3	4	5	6	7	8	9
Urine pH	6	6	6.5	6	7	5	6	6.5	6
Steady-state level ($\mu\text{g/ml}$)	0.056	0.11	0.08	0.21	0.51	0.11	0.08	0.03	0.034
Half-life (h)	6.68	11.92	9.58	15.05	15.77	8.88	9.43	7.67	8.18

Table 4 Pharmacokinetic parameters of mexiletine in patients with chronic renal failure

	Patients														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Urine pH (mean)	6	6.5	6.5	6	6	6	6	6.5	6	6	5.5	5.5	6	6	6
Steady-state level ($\mu\text{g/ml}$)	0.13	0.13	0.09	0.22	0.15	0.22	0.38	0.60	0.36	0.16	0.27	0.22	0.43	0.13	0.32
Half-life (h)	—	10.6	13.4	9.23	19	17.22	13.08	10.5	25.6	17.5	15.1	14.9	14.68	11.53	—

Table 5 Plasma concentration at steady-state and the half-life elimination of mexiletine (mean $\pm$ s.d.)

Group	n	Creatinine clearance (ml/min)	Plasma concentration	
			(8th day) ($\mu\text{g/ml}$)	$t_{1/2}$ (h)
I	9	> 75 ml	0.14 $\pm$ 0.15	10.35 $\pm$ 3.2
II	15	< 30 ml	0.25 $\pm$ 0.14	14.56 $\pm$ 4.47
A	8	< 10 ml	0.31 $\pm$ 0.15	15.69 $\pm$ 4.96
B	7	(10–30 ml)	0.19 $\pm$ 0.10	13.76 $\pm$ 3.76
P			(I-II) : NS (I-IIA) < 0.05 (I-IIB) : NS	(I-II) < 0.05 (I-IIA) < 0.025 (I-IIB) : NS

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(Received April 2, 1982
accepted April 26, 1982)