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THE PHARMACOKINETICS OF NORTRIPTYLINE IN PATIENTS WITH CHRONIC RENAL FAILURE

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1 The pharmacokinetics of single oral doses of nortriptyline were studied in twenty patients with chronic renal failure, eight of whom were receiving treatment with haemodialysis.

2 The median nortriptyline half-life was 25.2 h (range 14.5–140.0 h) and the median nortriptyline clearance was 32.3 l/h (range 8.1–122.0 l/h).

3 No differences were observed between the dialysed and non-dialysed groups.

4 Comparisons of nortriptyline half-life and clearance between the patients and groups of physically healthy subjects revealed no significant differences.

5 There was no significant linear correlation between age and either of these measurements. In the twelve patients not receiving haemodialysis there was no correlation between nortriptyline clearance and glomerular filtration rate.

6 Chronic renal failure is not associated with a significant alteration in nortriptyline metabolism as measured by its half-life or clearance, but the drug should nonetheless be used with caution, and monitored whenever possible. However, the marked inter-individual differences observed in nortriptyline half-life and clearance in patients with chronic renal failure may not be solely responsible for their unpredictable response to tricyclic antidepressant therapy, and other possible contributory factors are discussed.

Introduction

The prevalence of chronic renal failure might be as high as 19 per 100,000 and perhaps 4 per 100,000 might need dialysis (McCormick & Navarro, 1973). Although depressive symptoms are common in chronic renal failure (Tyler, 1968), there is disagreement over the actual incidence of formal primary depressive illness. Since haemodialysis patients who are psychiatrically ill have a diminished survival (Farmer, Snowden & Parsons, 1979), the need for effective psychiatric treatments seems particularly pressing.

In those cases where psychotropic medication is indicated, the choice of drug is limited by complications associated with their side-effects, and by the wish to avoid further dietary restrictions. Tricyclic antidepressants seem to be indicated in some cases (Cramand *et al.*, 1968; Levy, 1976), but the response to treatment has not been investigated systematically (Czaczkes & De Nour, 1978). Our clinical impression, like that of others (Buchanan *et al.*, 1977), is that the response is often disappointing. Possible reasons for this include the nature of the depressive illness, an abnormal elimination or protein binding of the drug, interactions between antidepressants and other medications, and the effects on mood of metabolic disturbances associated with chronic renal failure.

A series of studies on the metabolism of antidepressant drugs in chronic renal failure and its relevance to the outcome of depressive illness has been undertaken (Rosser *et al.*, 1979). One of these studies is described in this paper. Nortriptyline was chosen as a model because of its relatively uncomplicated metabolism and the abundance of kinetic data already available.

Methods

Twenty patients with chronic renal failure consented to participate in the study, for which approval was obtained from the Charing Cross Hospital Ethical Committee. The patients formed two groups: twelve who were being managed conservatively, and eight who were training for home dialysis and dialysed for

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Table 1 Details of the twelve patients not receiving haemodialysis.

Patient	*Age (years)*	*Sex*	*Weight (kg)*	*Cause of renal failure*	*^{51}Cr EDTA clearance (ml/min)*	*Drugs prescribed*	*Nortriptyline kinetics*	
							Half-life (h)	*Clearance (l/h)*
1	40	F	50	Hypertension	4.0	Gentamicin, diazepam, vancomycin, flucloxacillin, Orovite, folic acid	21.4	28.0
2	64	F	41	Polycystic disease	7.2	Distalgesic, flurazepam, trifluoperazine	48.8	15.2
3	18	M	48	Focal glomerulo-sclerosis	7.8	Nil	17.1	40.6
4	50	F	46	Nephro-calcinosis	25.0	Nil	14.5	122.0
5	60	M	98	Hypertension	53.0	Diazepam, bumetamide, Slow K	32.4	30.9
6	73	F	60	Papillary necrosis	7.9	Slow K, frusemide, hydralazine	23.5	34.4
7	56	F	56	Unknown	8.7	Nitrazepam, diazepam	66.0	18.3
8	50	F	63	Reflux nephropathy	14.0	Nitrazepam	22.4	32.8
9	65	F	38.5	Analgesic nephropathy	7.2	Chlorpheniramine, Orovite, folic acid, Distalgesic, nitrazepam, sodium bicarbonate, calcium resonium, vitamin D	29.6	16.1
10	41	M	65	Familial nephritis	9.2	Nil	23.0	41.2
11	42	M	54.2	Obstructive uropathy	6.8	Orovite, folic acid, Slow Na	15.7	14.1
12	61	M	64	Malignant hypertension	6.5	Orovite, folic acid, propranolol, frusemide, minoxidil	140.0	8.1

10 h twice weekly on Meltec Multipoint (1.0 m^2) kidneys.

Administration of drugs and blood sampling were performed according to the following protocol.

(a) Patients not being dialysed.
A single oral dose of 75 mg nortriptyline was administered at 09.00 h on the first day of the study. Heparinised venous blood samples (10 ml) were collected beforehand, and at 24, 30, 48, 54 and 72 h afterwards.

(b) Patients on dialysis.
These patients received a single oral dose of 75 mg nortriptyline immediately following dialysis. The blood sampling regime was followed as detailed above, the last sample being drawn prior to the next dialysis.

The plasma was separated and stored at −20°C until analysis. Plasma nortriptyline concentrations were determined by a specific gas-liquid chromatographic procedure with nitrogen-selective detection (Dawling & Braithwaite, 1978; Braithwaite, 1979).

From these measurements, a log-plasma nortriptyline concentration v time profile was constructed for each patient, and a linear least-squares regression analysis fitted to the terminal elimination phase (β-phase). From this line, plasma nortriptyline half-life ($T_{½}$) and total hepatic intrinsic clearance (Cl_i) were calculated using the formulae:-

$$T_{½} = \frac{0.693}{\beta} \quad \text{(h)} \qquad \text{Equation 1}$$

$$Cl_i = \frac{D}{(AUC)_\beta} \quad \text{(l/h)} \qquad \text{Equation 2}$$

where, assuming complete absorption and essentially hepatic metabolism, β is the gradient of the β-elimination phase, D is the dose administered, and $(AUC)_\beta$ is the area under the extrapolated β-slope and is a reliable approximation for the total area under the plasma concentration-time curve (Alexanderson, 1972a; Wilkinson & Shand, 1974).

Table 2 Details of the eight patients receiving haemodialysis

Patient	*Age (years)*	*Sex*	*Weight (kg)*	*Cause of renal failure*	*Drugs prescribed in addition to Orovite and folic acid*	*Nortriptyline kinetics*	
						Half-life (h)	*Clearance (l/h)*
13	37	M	53.5	Unknown	Amoxycillin calcium carbonate	28.0	64.9
14	47	M	80	Polycystic disease	Cephalexin, flucloxacillin	21.4	30.4
15	55	M	88.5	Analgesic nephropathy	Nil	34.8	31.8
16	55	M	77	Glomerulonephritis	Nil	31.0	34.9
17	22	F	48	Unknown	Nil	15.3	67.5
18	54	F	57.5	Polycystic disease	Calcium carbonate	30.1	95.8
19	29	M	68	Glomerulonephritis	Nil	21.4	44.3
20	63	F	59.5	Analgesic nephropathy	Paracetamol, nitrazepam	27.0	10.9

Nortriptyline half-life and clearance values obtained in this study were compared with previously published data using a Mann-Whitney U-test and considered significant if $P \leq 0.05$ (two-tailed).

Results

The patients were 10 male and 10 female, with a mean age of 49 years (range 18–73 years). Their ages, medication, glomerular filtration rates, nortriptyline plasma half-lives and clearances are shown in Tables 1 and 2. As the data were skewed, the median was used as a measure of central tendency and non-parametric statistics were applied. The median nortriptyline half-life was 25.2 h (range 14.5–140.0 h) and the median nortriptyline clearance was 32.3 l/h (range 8.1–122.0 l/h). Plasma nortriptyline half-life and clearance in the dialysed and non-dialysed patients did not differ (U = 47 for half-life; U = 29 for clearance).

The relationship between age and plasma nortriptyline half-life or clearance showed no significant linear correlation ($r = 0.27$ for half-life; $r = 0.38$ for clearance). There was no significant correlation between plasma nortriptyline clearance and glomerular filtration rate (^{51}Cr-EDTA clearance) in the twelve patients not being treated with haemodialysis.

Plasma nortriptyline half-life and clearance in these patients were compared with those in two groups of healthy subjects, the details of which are shown in Table 3, and in Figures 1 and 2. The first group were taken from the work of Alexanderson (1973). The clearance values reported by Alexanderson (1973) were calculated from the dose taken as hydrochloride salt and $(AUC)_\beta$ as free base (see Equation 2), so they were corrected by multiplying by 0.878. Because of the narrow age span (47–53 years) and homogeneity of the subjects (five pairs of monozygotic and six pairs of dizygotic twins), the patients were also compared to a group of 30 younger, non-related volunteers

Table 3 Comparison of nortriptyline kinetics in patients with chronic renal failure and healthy volunteers

Group	*Male/Female*	*Age (years) (mean ± s.d.)*	*Nortriptyline half-life(h) median (range)*	*Nortriptyline clearance (l/h) median (range)*
Alexanderson (1973)	12/10	50 ± 2	31.0 (18.3 – 93.3) U = 152	43.9 (14.1 – 100.0) U = 152
Healthy volunteers	19/11	26 ± 6	23.0 (14.8 – 51.3) U = 267	51.4 (15.6 – 115.0) U = 179*
Chronic renal failure	10/10	49 ± 15	25.2 (14.5 – 140.0)	32.3 8.1 – 122.0)

* With chronic renal failure group, $P < 0.05$ (Mann-Whitney U-test)

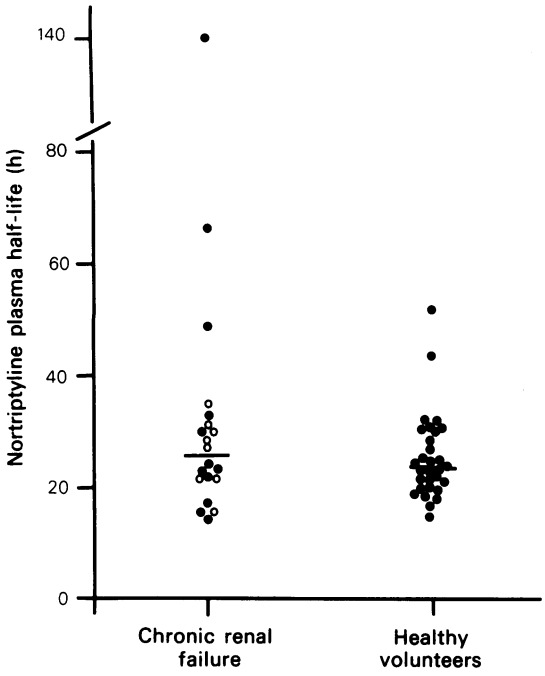

Figure 1 Individual values of nortriptyline plasma half-life in the 20 patients with chronic renal failure and the 30 healthy young volunteers. The medians are represented by the horizontal lines. Patients treated with haemodialysis are represented by O.

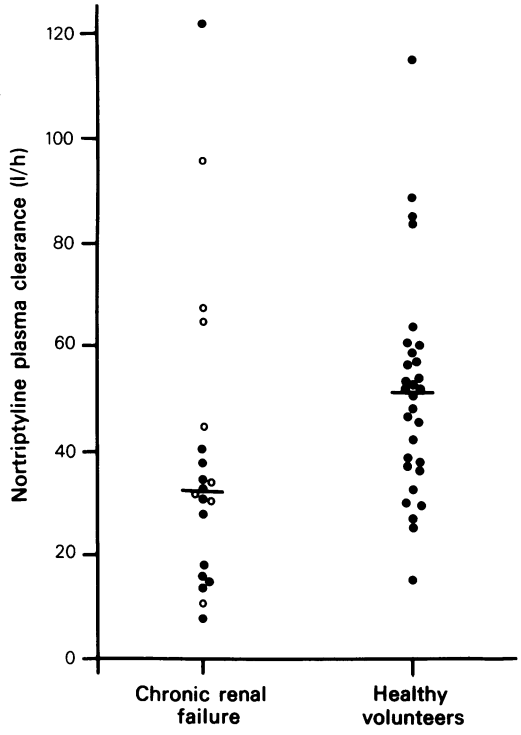

Figure 2 Individual values of nortriptyline plasma clearance in the 20 patients with chronic renal failure and the 30 healthy young volunteers. The medians are represented by the horizontial lines. Patients treated with haemodialysis are represented by O.

studied in this laboratory. No significant differences could be detected in nortriptyline kinetics between Alexanderson's (1973) volunteers and this group of patients. The patients with chronic renal failure also had similar nortriptyline half-lives to the younger volunteer group, but their nortriptyline clearances differed significantly when examined with the Mann-Whitney U-test ($U = 179$, $P < 0.05$).

Discussion

The findings of extreme inter-individual variability in both nortriptyline half-life and clearance in this study are similar to observations made by other workers in physically healthy subjects (Alexanderson, 1972b, 1973; Gram & Overø, 1975). The twenty patients with chronic renal failure showed a 10-fold variation in nortriptyline half-life (14.5–140 h), while plasma clearance varied 15-fold (8.1–122 l/h). The use of additional medication and the coexistence of other disease states in these patients may have enhanced the naturally occuring variability.

The similarity in nortriptyline pharmacokinetics between the patients treated with haemodialysis and those who were being managed conservatively was surprising, as these two treatment groups can exhibit marked differences with respect to drug handling (Levy, 1977).

To estimate the effect which chronic renal failure may have on nortriptyline kinetics, the nortriptyline half-life and clearance values obtained in this study were compared with previously published data in volunteers where these had been calculated similarly. No differences were detected in the comparison with similarly aged volunteers, although a significant difference in nortriptyline clearance was observed between the uraemic patients and the group of younger volunteers (Table 3, $U = 179$, $P < 0.05$). This finding suggested that there might be an age-related alteration in nortriptyline clearance. To investigate this phenomenon more thoroughly, an age and sex matching technique was used. The studies of volunteers (Alexanderson, 1972b, 1973; Gram & Overø, 1975; Dawling, Crome & Braithwaite, 1980) were searched preferentially for a partner of the same sex and similar age (within the same decade) as for each of the patients with chronic renal failure.

Table 4 Nortriptyline half-life and clearance in patients with chronic renal failure compared to age and sex matched physically healthy subjects

	Nortriptyline half-life (h) median (range)		*Nortriptyline clearance (l/h) median (range)*	
	Chronic renal failure	*Matching group*	*Chronic renal failure*	*Matching group*
All patients ($n = 20$)	25.2 (14.5 – 140.0)	30.9 (19.4 – 93.3)	32.3 (8.1 – 122.0)	42.6 (10.1 – 85.2)
	U = 138		U = 166	
Dialysed patients ($n = 8$)	27.5 (15.3 – 34.8)	23.7 (19.4 – 77.9)	39.9 (10.9 – 95.8)	46.0 (12.8 – 85.2)
	U = 31		U = 31	
Non-dialysed patients (n = 12)	23.3 (14.5 – 140.0)	32.5 (24.8 – 93.3)	29.5 (8.1 – 122.0)	38.5 (10.1 – 54.5)
	U = 50		U = 67	
Patients matched with volunteers (n = 11)	21.4 (14.5 – 66.0)	25.0 (19.4 – 93.3)	34.9 (14.1 – 95.8)	47.8 (14.1 – 85.2)
	U = 41		U = 51	

Eleven partners were found from these sources. The remaining nine were chosen from the data of Braithwaite, Montgomery & Dawling (1978) in-depressed, but otherwise healthy subjects.

The Mann-Whitney U-test showed there to be no significant differences between the groups with respect to nortriptyline half-life or clearance. This was true whether the groups were analysed together, or as separate dialysed and non-dialysed groups. These results together with the group medians and ranges are shown in Table 4. It seemed possible that the nine depressed patients included in the matching group could have abnormal nortriptyline kinetics as they had been preselected by their previous poor response to antidepressant therapy (Braithwaite *et al.*, 1978). Therefore the analysis was repeated using only the eleven patients matched with volunteers. Again, no significant differences were observed (Table 4). These results agree with the finding that there is no correlation between age and notriptyline half-life or clearance in this study and in previous studies with nortriptyline (Braithwaite *et al.*, 1978; Dawling *et al.*, 1980).

This investigation demonstrated no predictable alteration in nortriptyline kinetics in chronic renal failure as measured by the drug's half-life and clearance. However, the variability in the results was extreme, and the positive skew of both the half-life and clearance distributions was particularly noticeable in the chronic renal failure group (Figures 1 and 2). There were no common characteristics amongst the patients responsible for the deviations from the normal distribution in terms of age, sex, drug ingestion, and aetiology or severity of renal failure.

An inverse relationship between the plasma clearance of a single oral dose and the steady-state concentration of nortriptyline ultimately achieved has been demonstrated in many circumstances (Alexanderson, 1973; Braithwaite *et al.*, 1978; Dawling *et al.*, 1980), but it has not yet been tested in chronic renal failure. If this relationship holds good, then ten of the patients in this study (with clearances above 60 l/h or below 20 l/h) would achieve steady-state concentrations outside the accepted therapeutic range on a 75 mg daily dose (Åsberg *et al.*, 1971; Kragh-Sørensen *et al.*, 1976; Ziegler *et al.*, 1976). The incidence of abnormal nortriptyline clearance values in this random sample of patients with chronic renal failure suggests that their response to this drug would be poor, as low plasma concentrations are ineffective, and high concentrations are associated with a diminished antidepressant effect in addition to side-effects (Åsberg, 1974; Kragh-Sørensen, 1978; Ziegler *et al.*, 1978). However, it is unlikely that inappropriate plasma concentrations of nortriptyline itself are the sole explanation for the poor response seen to this drug in patients with renal failure, and other facets of nortriptyline metabolism should be explored.

Nortriptyline is metabolised by hepatic demethylation and hydroxylation (von Bahr, 1972). In chronic renal failure, hepatic oxidation mechanisms are usually unaltered (Reidenberg, 1977b), and this is confirmed in this study by the lack of a relationship between nortriptyline kinetics and glomerular filtration rate. This is in contrast to the situation with drugs which are excreted primarily by renal mechanisms, where dosage regimes must be adjusted according to individual glomerular filtration rates (Dettli, Spring & Habersang, 1970). Normally, the majority of nortriptyline is excreted following glucuronide conjugation of the hydroxylated metabolite, 10-hydroxynortriptyline (Alexanderson & Borgå, 1973), and it is possible that these compounds accumulate in renal insufficiency. The hydroxymetabolites of both nor-

triptyline and imipramine have recently been shown to be active with respect to synaptosomal uptake of neuro-transmitter amines, and it is thought likely that their presence influences the clinical effectiveness of these drugs (Bertilsson, Mellström & Sjöqvist, 1979; Potter *et al.*, 1979).

It is also possible that the drug's ability to bind to serum proteins is in some way diminished (Reidenberg, 1977a). Since this drug is normally highly protein bound (Borgå *et al.*, 1969; Alexanderson & Borgå, 1972; Brinkschulte & Breyer-Pfaff, 1979) and only the free fraction is pharmacologically active, a small decrease in binding could produce apparent sensitivity to the drug. The possibilities of an alteration in nortriptyline protein binding or an abnormality of hydroxylated metabolites in chronic renal failure are currently being investigated.

In conclusion, chronic renal failure is not associated with a predictable alteration in nortriptyline pharmacokinetics, and it is not possible therefore to recommend an amendment of the usual dosage regime. However, the extreme inter-individual variability in drug handling highlights the need for the use of predictive tests, such as single oral dose clearance or 24 h plasma concentration measurements (Alexanderson, 1972a,b; Cooper & Simpson 1978; Montgomery *et al.*, 1979; Dawling *et al.*, 1980). Moreover, the potential danger of side-effects and the difficulty in their diagnosis in patients with chronic renal failure dictate that plasma concentrations of antidepressant drugs be monitored whenever possible.

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