THE EFFECT OF RENAL DISEASE ON THE PHARMACOKINETICS OF DIETHYLCARBAMAZINE IN MAN

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- 1 The pharmacokinetics of diethylcarbamazine (DEC) were studied in twelve patients with chronic renal function impairment.
- 2 Selected pharmacokinetic parameters, plasma half-life ($T_{1/2}$), area under the plasma concentration-time curve (AUC), elimination rate constant (Kel) and 24 h urinary excretion were regressed versus parameters indicative of renal function.
- 3 Significant negative correlations were observed between creatinine clearance and both plasma $T_{1/2}$ and $\log_{10} T_{1/2}$.
- 4 Significant positive correlations were obtained between (a) creatinine clearance and elimination rate constant of DEC and (b) reciprocal serum creatinine and $1/T_{1/2}$. Creatinine clearance was significantly and positively correlated with 24 h urinary excretion of DEC.
- 5 No significant correlations were observed between age, sex or weight and renal function but DEC excretion did appear to decrease with increasing urinary pH.
- 6 Plasma half-life, and area under the plasma concentration-time curve were increased and 24 h urinary excretion of DEC was significantly reduced in patients with chronic renal function impairment, compared with normal volunteer subjects receiving an identical dosage of DEC at acidic urinary pH.

Introduction

Diethylcarbamazine (DEC) has been used in the treatment of human filariasis for over 30 years (Hawking, 1950). The pharmacokinetics of DEC have received little attention although earlier studies in animals (Bangham, 1955; Faulkner & Smith, 1971; Edwards *et al.*, 1981a) indicated that DEC is extensively metabolised. Recent studies in man (Edwards *et al.*, 1981b) have shown that DEC is excreted unchanged in the urine to a significant extent and further that its renal elimination is pH dependent. Approximately 70% of a dose of DEC is excreted in the urine at pH 5.0 and less than 10% at a urine pH of 8.0 (Adjeon-Yamoah *et al.*, 1981).

Patients with filarial infections may have, in addition, an impairment of renal function and we have therefore studied the pharmacokinetics of DEC in patients with moderate and severe degrees of renal impairment.

Methods

Patients studied

Twelve patients with chronic renal impairment were studied. All gave their informed consent and the study was approved by the Royal Liverpool Hospital Ethical Committee. All patients were attending the renal clinic at the Royal Liverpool Hospital.

The clinical details including other drug therapy are shown in Table 1. Urine output ranged between 1100 and 2100 ml/day. Renal function had been stable over the preceding 6 months; no patient was in cardiac failure, and results of liver function tests were within normal limits. Creatinine clearance was determined on one occasion over a 24 h period, 1 week prior to the study. For the purposes of this study, patients with a creatinine clearance of less than 25 ml/min were considered to have severe renal failure, and those whose creatinine clearance was between 25 and 60 ml/min, moderate renal failure.

Protocol

After a light breakfast the bladder was emptied and each patient ingested 50 mg diethylcarbamazine

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Table 1 Clinical details of the patients studied

Patient	Age (years)	Sex	Weight (kg)	Creatinine clearance (ml min ⁻¹)	Serum creatinine (μmol l ⁻¹)	Aetiology of renal failure	Other illnesses	Concurrent drug therapy
1	57	M	62	60	162	Proliferative glomerulonephritis	None	Azathioprine Prednisolone
2	29	M	86	56	134	Hypertension	None	Labetalol Frusemide
3	22	F	62	50	146	Hypoblastic kidney	Mild hypertension	Nadolol
4	53	M	68	31	362	Obstructive uropathy	None	Sodium bicarbonate
5	60	M	68	28	465	Renal tuberculosis	Hypertension Angina pectoris	Labetalol Bendrofluzide
6	47	M	64	24	307	Hypertension	None	Labetalol
7	53	M	70	22	329	Hypertension	None	Labetalol
8	22	F	67	20	265	Systemic lupus erythematosus	None	Frusemide Prednisolone Azathioprine Cimetidine
9	55	F	52	10	574	Polycystic kidneys	Mild hypertension	Bendrofluzide Methyldopa Sodium bicarbonate
10	43	F	70	7	609	Diabetic nephropathy	Hypertension	Metoprolol Insulin Frusemide Metoclopramide Frusemide
11	58	M	55	5	850	Hypercalcaemia renal osteodystrophy	Coronary artery disease	
12	52	F	65	4	780	Analgesic nephropathy	None	None

1–5 Moderate chronic renal failure; 6–12 Severe chronic renal failure.

citrate (25 mg DEC free base) as a single tablet with 50 ml of water. Lunch was given 4 h after dosing. Venous blood was sampled predose and at 1.5, 3, 6, 9, 12 and 24 h after dosing with the initial samples being taken through an indwelling venous catheter. Plasma was stored at -20°C after centrifugation. The patients were ambulant throughout the study. All urine passed from 0 to 24 h was collected, volume and pH measured and aliquots stored at -20°C until the time of analysis. The urine pH of all patients, measured immediately after collection, was between 5.0 and 6.0 except for patient No. 9 whose urine pH was 7.0.

A similar single dose study of DEC was performed in four healthy male volunteers (aged between 23 and 45 years) who were taking no other drug therapy. In this study the urine pH was kept between 5.0 and 5.5 with the use of ammonium chloride tablets (Beckett & Rowland, 1965) in order to provide a closer comparison with the renal failure patients.

Materials

Diethylcarbamazine citrate was a gift from Dr D.B.A. Hutchinson, Department of Clinical Immunology, The Wellcome Research Laboratories, Beckenham, Kent. Gas-liquid chromatographic packing material was obtained from Phase Separations Ltd, Queensferry, Clwyd, N. Wales. A Perkin-Elmer gas liquid chromatograph model F17 equipped with a nitrogen detector was used. Phenmetrazine theoclate, the internal standard, was donated by Berk Pharmaceuticals Ltd, Guildford, Surrey. All reagents used for analysis were obtained from B.D.H. Ltd, Poole, Dorset, England and were of analytical grade.

Analysis of DEC and DEC-N-oxide

The gas liquid chromatographic method of Allen *et al.* (1979) was used as modified by Edwards *et al.* (1981a) for the analysis of DEC in plasma and urine.

Diethylcarbamazine-N-oxide concentrations in urine were determined following incubation of urine samples (0.5 ml) at 37°C with titanium trichloride (30% in HCl) for 1 h to permit complete reduction of DEC-N-oxide to diethylcarbamazine which was analysed as above. N-oxide levels were then calculated by difference.

Calculations

The terminal half-life $T_{1/2}$ of diethylcarbamazine was calculated by linear regression of the terminal portion of the plasma concentration versus time curve. The area under the plasma concentration-time curve from $0-\infty$ (AUC) was calculated from the following equation (Gibaldi & Perrier, 1975):

$$\text{AUC}_{0-\infty} = \text{AUC}_{0-24} + 1.44 \times C_{p24} \times T_{1/2}$$

AUC_{0-24} is the area under the plasma concentration time curve from 0 to 24 h (calculated by the trapezoidal method) and C_{p24} is the plasma concentration of DEC at 24 h (Gibaldi & Perrier, 1975). The rate constant of elimination of DEC (Kel) was obtained using the relationship:

$$\text{Kel} = \frac{0.693}{T_{1/2}}$$

Statistical analysis of mean differences was done using Student's *t*-test. Correlations between the various results were tested using linear regression analysis.

Table 2 Plasma half-life, $\text{AUC}_{0-\infty}$ and urinary recovery of DEC base and its N-oxide in the 12 patients

Patient	Creatinine clearance (ml min^{-1})	$T_{1/2}$ (h)	$\text{AUC}_{0-\infty}$ ($\mu\text{g l}^{-1} \cdot \text{h}$)	24 h urinary excretion of DEC base (mg)	24 h urinary excretion of DEC N-oxide base (mg)
*1	60	6.0	1298	7.50	3.20
2	56	5.0	765	11.62	11.00
3	50	3.5	700	8.52	7.63
**4	31	13.0	1783	5.90	1.50
5	28	11.0	2538	5.62	2.81
6	24	10.0	3913	5.25	0.00
7	22	13.0	1448	4.47	5.98
8	20	13.0	2748	5.48	4.48
*9	10	32.0	3345	1.68	2.30
10	7	9.0	525	4.20	7.63
11	5	14.0	1940	3.30	4.82
12	4	15.0	1540	1.34	2.66

*urine pH = 7, **urine pH = 6.0.

Table 3 Comparison of results between the two groups of patients and the healthy volunteers (mean $\pm$ s.d.)

	DEC $T_{1/2}$ (h)	AUC ₍₀₋₂₄₎ ($\mu\text{g l}^{-1}\text{h}$)	24 h urinary excretion of DEC base (mg)	24 h urinary excretion of DEC N-oxide (mg)
Healthy volunteers (acidic urine pH)	2.7 ± 0.35	348 ± 145	16.13 ± 2.26	1.14 ± 0.88 NS
Patients with moderate renal failure	7.7 ± 4.1 $P < 0.05$	2830 ± 1530 $P < 0.05$	7.8 ± 2.43 $P < 0.001$	5.22 ± 3.97 NS
Patients with severe renal failure	15.14 ± 7.7 $P < 0.001$	3410 ± 2170 $P < 0.001$	3.33 ± 1.80 $P < 0.001$	3.99 ± 2.54 NS

The P values refer to comparisons between the means of healthy volunteers and each group of patients.

Results

Plasma half-life, AUC and urinary excretion of DEC are shown in Table 2 for the individual patients. The means of these values are shown in Table 3 compared to the figures for the four healthy volunteers. The mean plasma half-life in each group of patients was significantly longer than in the normal volunteers ($P < 0.01$). The mean plasma half-life in the patients with severe renal failure was (15.1 ± 7.7 h, mean $\pm$ s.d.) significantly longer than in the patients with moderate renal impairment (7.7 ± 4.1 h, $P < 0.05$). Figure 1 shows the plasma concentration-time curve for DEC in a normal volunteer, in a patient with severe renal failure (creatinine clearance 20 ml/min) and in a patient with moderate renal failure (creatinine clearance 56 ml/min).

Concentrations of DEC in plasma were significantly higher in patients than in the normal volunteers as shown in Table 3. The mean plasma DEC concentration at 1.5 h after dosing was $45.1 \pm 9.1 \mu\text{g/l}$ in the healthy volunteers compared to $183.8 \pm 88.3 \mu\text{g/l}$ in the patients ($P < 0.001$). The figures at 3 h were $50.0 \pm 17.2 \mu\text{g/l}$ and $201.5 \pm 77.2 \mu\text{g/l}$ respectively ($P < 0.001$).

The area under the DEC plasma concentration-time curve was significantly greater ($P < 0.05$) in each of the two groups of patients compared with that obtained in the healthy volunteers (Table 3). The mean areas of the patients with severe renal impairment did not differ significantly from those of the patients with moderate renal impairment.

The amount of DEC excreted unchanged in 24 h in each group of patients was significantly less than that in the healthy volunteers ($P < 0.001$, Table 3). The patients with a moderate degree of renal impairment

Figure 1 Plasma concentrations of diethylcarbamazine in a patient with severe (▼) and moderate (●) renal impairment compared with (■) a normal subject with acidic urine.

excreted significantly more DEC ($P < 0.01$) in 24 h than those with severe impairment. No significant differences in the urinary excretion of DEC *N*-oxide were observed.

Table 4 gives the correlations of important independent variables in the patients. There was a significant negative correlation in these subjects between the degree of renal impairment, as measured by creatinine clearance, and both plasma half-life of DEC ($r = -0.63$, $P < 0.05$) and its logarithm ($r = -0.78$, $P < 0.01$) and a significant positive correlation between the creatinine clearance and the rate constant of elimination of DEC from the plasma ($r = 0.78$, $P < 0.01$, Figure 2). The urinary excretion of DEC was positively correlated with creatinine clearance ($r = 0.90$, $P < 0.001$). The reciprocal of the serum creatinine concentration correlated strongly with the reciprocal of the DEC plasma half-life ($r = 0.86$; $P < 0.001$, Figure 3). Plasma half-life was correlated with increasing urinary pH ($r = 0.79$, $P < 0.01$). There was a significant negative correlation between the amount of DEC excreted in 24 h and the plasma half-life of DEC ($r = -0.74$, $P < 0.01$). There was no correlation between the creatinine clearance and the area under the DEC concentration-time curve ($r = 0.34$; $P > 0.5$) but there was a weak negative correlation between the patient's weight and the DEC half-life ($r = 0.57$). There was no correlation between the age of the patient and the plasma half-life of DEC ($r = 0.41$, $P > 0.1$).

Discussion

Diethylcarbamazine is eliminated in man by both hepatic metabolism and more significantly by renal excretion. Renal disease may therefore be expected

Figure 2 Graph indicating relationship between creatinine clearance and elimination rate constant in 12 subjects.

Figure 3 Graph indicating relationship between $1/\text{serum creatinine}$ and $1/T_{1/2}$ in 12 subjects.

Table 4 Correlation of independent variables in the patients

Independent variables (Ordinate)	Correlated variable (Abcissa)	Correlation coefficient	Slope of regression line	Intercept on abscissa	P value
Creatinine clearance (ml min ⁻¹)	$T_{1/2}$ (h)	-0.63	-0.23	18.2	< 0.05
	log $T_{1/2}$	-0.78	-0.009	1.28	< 0.01
	Kel (h ⁻¹)	+0.78	+0.002	0.027	< 0.01
	AUC _{0-∞} (μg l ⁻¹ h)	-0.34	-18.7	2373	NS
	24 h urinary excretion (mg)	+0.90	+0.13	1.96	< 0.001
Reciprocal serum creatinine (μmol ⁻¹ l)	$1/T_{1/2}$ (h ⁻¹)	+0.86	+27.47	0.018	< 0.001
Urine pH	$T_{1/2}$	0.79	18.33	-91.18	< 0.01
24 h urinary excretion (mg)	$T_{1/2}$	-0.74	-1.89	22.2	< 0.01
Age (years)	$T_{1/2}$	+0.41	+0.22	2.06	NS
Weight (kg)	$T_{1/2}$	-0.57	-0.49	44.3	NS

to delay the elimination of the drug from the body. This is confirmed by our results which show that the plasma $T_{1/2}$ of DEC is prolonged and its 24 h urinary excretion is considerably reduced in patients with moderate and severe degrees of renal failure. The greater the degree of renal impairment the slower the rate of elimination of DEC from the body. However, it is noted that patient 9, in whom the longest plasma DEC $T_{1/2}$ (32 h) was observed, did not have the poorest renal function. Other factors may also be important in the elimination of DEC from the body. It is likely that the abnormally slow elimination of the drug in this patient was due to the high urine pH (7) resulting from sodium bicarbonate therapy. Patient 4 had a longer plasma $T_{1/2}$ than expected (13 h) since his creatinine clearance was 31 ml/min. However, he too had a less acidic urine (pH 6.0).

Changes in plasma protein binding (Reidenberg, 1976) or hepatic elimination (Fabre & Balant, 1976) may relate to uraemia. Unpublished results from this laboratory showed that DEC binding to plasma from subjects with normal renal function ranged from 1.6 to 4.4%. The influence of renal function impairment on the hepatic metabolism of DEC was not examined in this study.

We have recently shown that the elimination of DEC is pH dependent (Adjepon-Yamoah *et al.*, 1981). In healthy volunteers the plasma elimination $T_{1/2}$ and the area under the concentration v time curve of DEC are greatly increased when the urine pH changes from acidic to alkaline. The significantly

positive correlation between the urine pH and the plasma DEC $T_{1/2}$ in this study supports the view that the high pH of the urine may partially contribute to the very long plasma DEC $T_{1/2}$ in patients 4 and 9. The contribution of concurrent drug therapy to the delayed elimination of DEC from the plasma in the patients is difficult to assess since the drugs were not the same in all patients. One patient was not on any drug therapy at the time of the study yet the plasma DEC $T_{1/2}$ was the same as those of other patients on multiple drug therapy.

DEC accumulates in patients with onchocerciasis with renal impairment during repeated administration. The degree of accumulation of the drug will be much greater in an alkaline urine, resulting from the ingestion of largely vegetarian diet. These elevated plasma levels may predispose to toxicity and the dose of DEC in such circumstances should be greatly reduced.

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