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Pharmacokinetics and renal elimination of desferrioxamine and ferrioxamine in healthy subjects and patients with haemochromatosis

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1 Desferrioxamine mesylate (DM) (10 mg kg^{-1} = 15.24 μmol kg^{-1}) was given by intramuscular injection to five healthy subjects and to six patients with haemochromatosis, after informed consent.

2 Desferrioxamine (DFA), ferrioxamine (FeA), aluminoxamine (AlA), aluminium (Al) and iron (Fe) were measured in plasma, before and 10, 20, 30, 60 min and 2, 4, 6, 8, 12 h after DM injection and in urine collected over a 6 h period the day before and the day of administration.

3 The predominant form in plasma from control subjects was DFA whereas FeA predominated in plasma from patients. In controls, rapid and slow phases of decline in plasma DFA concentrations were found, with half-lives of 1.0 h and 6.1 h, respectively. In the patients, only a single phase of decline was observed, with a half-life of 5.6 h. Total clearances of DFA were 296 ml h^{-1} kg^{-1} in controls and 239 ml h^{-1} kg^{-1} in patients.

4 The amount of FeA eliminated in urine during 6 h was significantly lower in controls (8.0 ± 4.6 μmol) than in patients (129.2 ± 40.0 μmol), with respective renal clearances estimated over 6 h of 516 ml h^{-1} kg^{-1} and 1,716 ml h^{-1} kg^{-1}. DFA elimination was similar in both groups and its renal clearance estimated over 6 h was 91 ml h^{-1} kg^{-1} in controls and 85 ml h^{-1} kg^{-1} in patients.

5 Since there was no overlap in the 1 h DFA/FeA plasma ratio between controls and patients, this might be useful as an index of iron overload.

Keywords desferrioxamine ferrioxamine haemochromatosis pharmacokinetics

Introduction

Desferrioxamine mesylate (Desferal®, Ciba,) (DM) is the most effective chelator available for the treatment of iron (Fe) overload in man. Its efficacy is usually assessed from the increase in urinary Fe elimination. Only incomplete pharmacokinetic data on DM are available (Summers *et al.*, 1979).

The colorimetric assay method of Meyer-Brunot & Keberle (1967) used previously is insensitive and high performance liquid chromatography has yet to be adapted for the measurement of desferrioxamine (DFA) in biological samples (Cramer *et al.*, 1984).

Using an indirect micromethod (Allain *et al.*, 1986), we have made a comparative study of the pharmacokinetics of DFA and ferrioxamine (FeA) in healthy subjects and in patients with haemochromatosis, after a single 10 mg kg^{-1} (15.24 μmol kg^{-1}) intramuscular dose of DM.

Methods

Five healthy subjects, three males and two females (age 37.2 ± 5.8 years (mean ± s.d.), body weight 61.8 ± 9.8 kg) and six male patients with haemochromatosis (age 46.7 ± 13.9 years, body weight 69.5 ± 12.4 kg) received, in the morning, a single intramuscular injection of 10 mg kg^{-1} (15.24 μmol kg^{-1}) of DM in the upper outer quadrant of the buttock. Patients and controls were not confined to bed and could come and go in the care unit between the blood withdrawals. Informed consent was obtained from each individual. The diagnosis of haemochromatosis was based upon clinical and biological assessments (Table 1). All of the control subjects had a serum ferritin level under 100 μg l^{-1}. Serum creatinine levels were normal both in controls and patients.

Blood samples were drawn before, and at 10, 20, 30, 60 min, 2, 4, 6, 8, and 12 h after DM administration. Blood collected in heparinized tubes was centrifuged within 1 h to avoid haemolysis and stored at 4° C until assay. Urine was collected over a 6 h period the day before and the day of DM administration.

DFA, FeA and AlA in plasma and urine, were measured by an indirect micromethod based upon selective extraction in benzyl alcohol of FeA, AlA and DFA after its conversion to FeA by an excess of iron and measurement of iron and aluminium by graphite furnace atomic absorption spectrometry (Allain *et al.*, 1986). Aluminium (Al) and (Fe) were measured by inductively coupled plasma emission spectrometry (Mauras & Allain 1985).

Maximum concentration (C_{max}), time to maximum concentration (t_{max}), area under curve (AUC), total clearance (CL = DOSE/AUC), volume of distribution (V_{area} = CL/k), and half-lives ($t_{½}$) were calculated using the Stripe pharmacokinetic programme of Johnston & Woollard (1983). Renal clearances were calculated over 6 h by dividing the amount excreted in urine by the corresponding AUC values.

Results

The time courses of plasma DFA and FeA concentrations after intramuscular administration of 15.24 μmol kg^{-1} DM to controls and patients with haemochromatosis are shown in Figures 1 and 2. Comparison of these data clearly shows that the predominant form in plasma was DFA in controls and FeA in patients with haemochromatosis. Table 2 shows the pharmacokinetic parameters derived from these curves.

Peak plasma DFA concentrations were higher in controls (15.5 ± 1.8 μmol l^{-1}) than in patients (7.0 ± 5.3 μmol l^{-1}), with t_{max} at 0.5 and 1.0 h respectively (Figure 1). The shape of the curves was different: in controls, rapid and slow phases of decline in DFA plasma concentrations were found with respective half-lives of 1.0 and 6.1 h whereas in patients only one phase of decline with a half-life of 5.6 h was observed. The total clearance and the distribution volume (V_{area}) for DFA were similar in controls and patients and renal clearances were about one third of total clearance in controls and patients (Table 2).

Peak plasma FeA concentrations were very different in controls (3.7 ± 2.6 μmol l^{-1}) and patients (15.7 ± 2.9 μmol l^{-1}) with the same t_{max} (1 h). The $t_{½}$ of decline was approximately the same in controls (fast decline 2.4 h and slow decline 5.9 h) and in patients (4.6 h) but the AUC values were significantly different (29.4 and 131.8 μmol h l^{-1} in controls and patients, respectively). Renal clearances were also quite different: 516 ml h^{-1} kg^{-1} in controls and 1,716 ml h^{-1} kg^{-1} in patients.

The DFA/FeA concentration ratios in plasma were significantly different in controls and in patients (Figure 3). For example, 1 h after DM dosage the ratios were 4.1 ± 1.9 and 0.4 ± 0.2 in controls and patients, respectively.

Table 3 shows the urinary elimination of DFA, FeA, AlA, Fe and Al over a period of 6 h. The total excretion of DFA + FeA + AlA was significantly higher ($P < 0.05$) in patients (307.7 ± 72.5 μmol l^{-1}) than in controls (220.8 ± 48.4 μmol l^{-1}). The amount of FeA eliminated in Fe-overloaded patients (129.2 ± 40.0 μmol) was considerably higher than in controls (8.0 ± 4.6 μmol). DFA elimination was not significantly different between controls (212.6 ± 45.3 μmol) and patients (178.5 ± 55.2 μmol) and AlA elimination was negligible.

Fe elimination in controls over a 6 h period was 0.1 ± 0.1 μmol before DM administration and 8.3 ± 5.1 μmol after. In patients, it was 1.2 ± 1.1 μmol before DM administration and 121.2 ± 38.2 μmol after.

Al elimination was low in both controls and patients, but increased after DM administration.

Discussion

Compared with controls, patients showed significant increases in plasma FeA concentrations and AUC (Figure 2) resulting from the transformation of DFA to FeA by iron overloaded tissues. This increase in FeA formation in patients explains the lower C_{max} of DFA (Figure 1) and the absence of the fast DFA distribution phase.

Table 1 Patients with idiopathic haemochromatosis. Clinical features and laboratory data

	Patient 1	*Patient 2*	*Patient 3*	*Patient 4*	*Patient 5*	*Patient 6*
Age (years)	61	61	26	42	38	52
Clinical features[1]	P/H/NIDD/A/G	P/H/NIDD/A/G	P/H/IDD/G	P/H/IGT	P/H/C/A/G	P/H/NIDD/A
Serum iron (μmol l^{-1})	31	34	33	46	43	40
Transferrin saturation (%)	97	82	94	96	100	93
Serum ferritin (μg l^{-1})	1560	883	9096	3673	N.D.	1363
C.T. count[2] Hounsfield units (normal $\leq$ 65)	N.D.	72	100	100	N.D.	90
% Iron loaded hepatocytes[3]	100	75	100	80	100	100
Liver iron concentration (μmol $100g^{-1}$) (normal $\leq$ 3.6)	25.4	N.D.	36.6	N.D.	60.0	N.D.
Liver cirrhosis = C fibrosis = F	C	C	C	F	F	C
HLA antigens	A2 A3 B12 B35	A2 A. B. B.	A3 A3 B7 B40	A3 A. B7 B.	A3 A9 B7 B14	A3 A3 B7 B14
Phlebotomies litres C=continued	13.2 C	no	19.2 C	6.0 C	110.0	23.0
Al.A.T.[4] normal < 22	53	20	229	218	29	47
5′ Nucleotidase normal < 17	12	6	12	7	6	7
G.G.T.[5] normal < 37	150	53	119	220	93	25
Prothrombin time normal = 100	62	56	70	62	75	91

[1] P = Pigmentation H = hepatomegaly IDD = insulin dependent diabetes mellitus NIDD = non insulin dependent diabetes mellitus IGT = impaired glucose tolerance A = arthropathy C = cardiomyopathy G = hypogonadism N.D. = Not determined.
[2] C.T. = Computerized tomography count.
[3] Measured by histochemical colouration on liver biopsies.
[4] Al.A.T. = Alanine amino-transferase.
[5] G.G.T. Gamma-glutamyl-transferase.

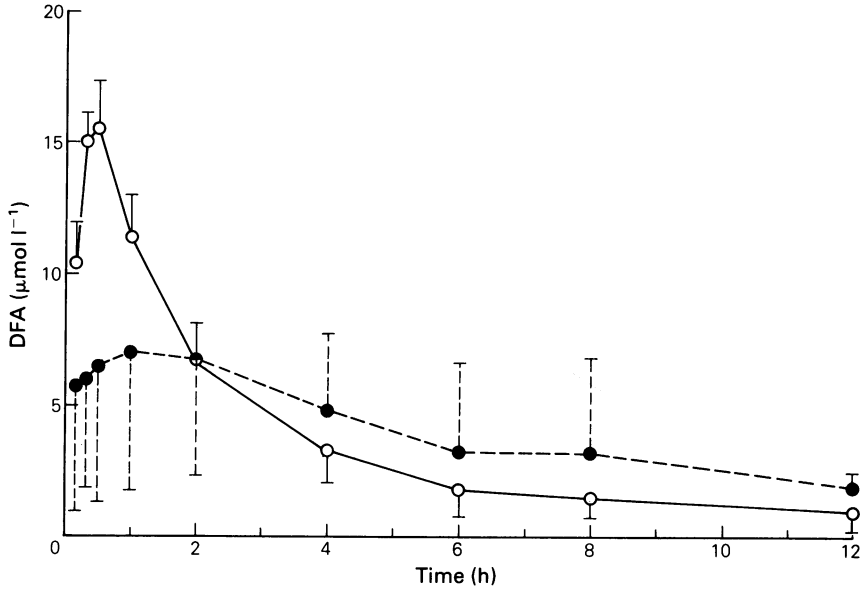

Figure 1 Mean (± s.d.) plasma concentrations of DFA in five healthy subjects (——) and in six patients with haemochromatosis (-----) after 10 mg kg^{-1} (15.24 μmol kg^{-1}) intramuscular injection of desferrioxamine mesylate (DM).

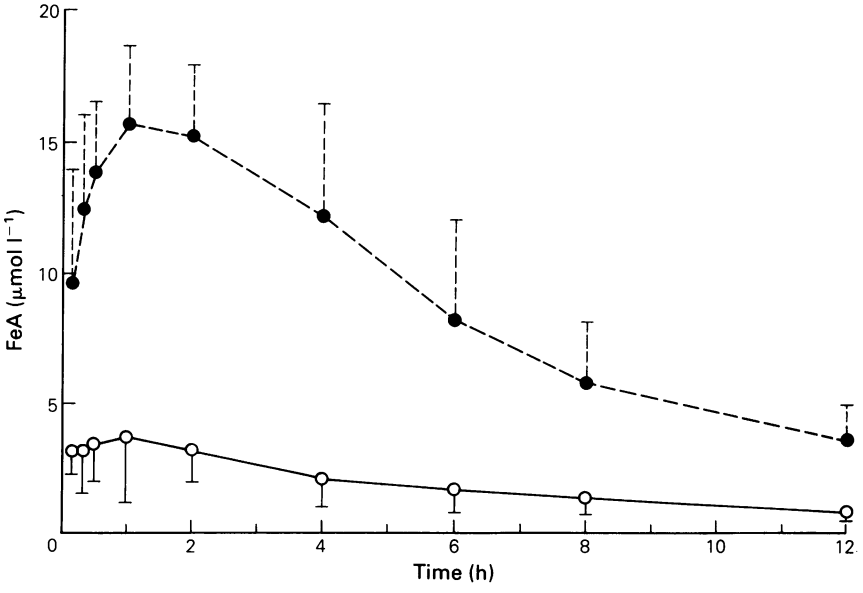

Figure 2 Mean (± s.d.) plasma concentrations of FeA in five healthy subjects (——) and six patients with haemochromatosis (-----) after 10 mg kg^{-1} (15.24 μmol kg^{-1}) intramuscular injection of desferrioxamine mesylate (DM).

Since there was no overlap between control and patient values of the DFA/FeA concentration ratio in plasma, particularly at one hour after DM injection, this index may be useful in the diagnosis of iron overload. However the value of such a test needs to be assessed in a larger series of controls and patients with haemochromatosis and other liver diseases.

Table 2 Pharmacokinetic parameters describing the disposition of DFA and FeA in five healthy subjects and six patients with haemochromatosis after a 15.24 μmol kg^{-1} intramuscular injection of desferrioxamine mesylate. (Values are mean ± s.d.)

	DFA Controls	*DFA Patients*	*FeA Controls*	*FeA Patients*
C_{max} (μmol l^{-1})	15.5 ± 1.8	7.0 ± 5.3	3.7 ± 2.6	15.7 ± 2.9
t_{max} (h)	0.5	1.0	1.0	1.0
$t_{½}$ fast phase (h)	0.98	Absent	2.35	Absent
$t_{½}$ slow phase (h)	6.06	5.58	5.85	4.63
AUC (0–∞) (μmol l^{-1} h)	51.5	63.7	29.4	131.8
Total clearance (ml h^{-1} kg^{-1})	296	239	*	*
Renal clearance (l h^{-1} kg^{-1})	91	85	516	1,716
V_{area} (l kg^{-1})	2.59	1.92	*	*

* not calculated (FeA is a metabolite).

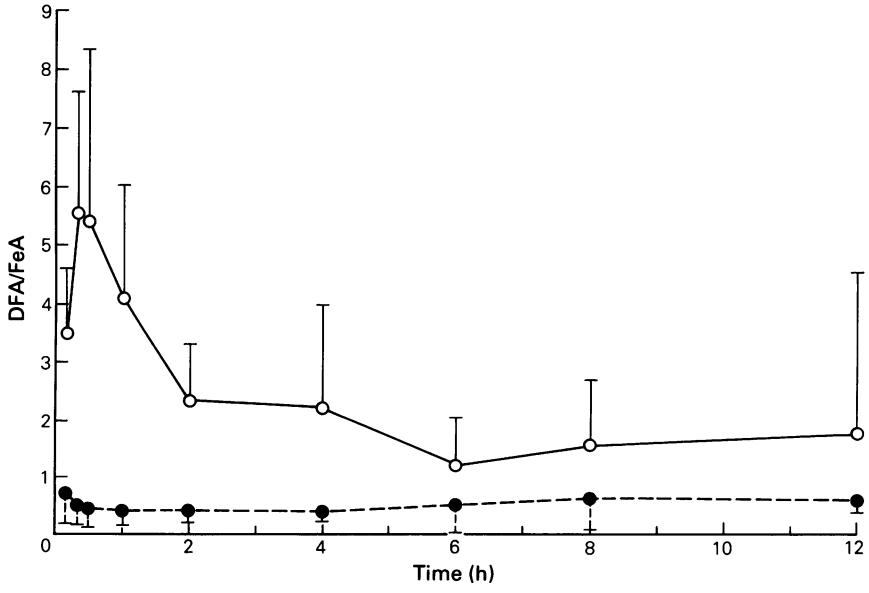

Figure 3 Mean (± s.d.) plasma DFA/FeA ratio in five healthy subjects (——) and in six patients with haemochromatosis (-----) after 10 mg kg^{-1} (15.24 μmol kg^{-1}) intramuscular administration of desferrioxamine mesylate (DM).

Table 3 Urinary elimination (6 h) of DFA, FeA, AlA, Fe, Al in controls and in patients with haemochromatosis before and after intramuscular administration of desferrioxamine mesylate (DM) 15.24 μmol kg^{-1} body weight. (Values are mean ± s.d.)

	Controls Before	*Controls After*	*Patients Before*	*Patients After*
DFA+FeA+AlA (μmol)	0	220.8 ± 48.4	0	307.7 ± 72.5
FeA (μmol)	0	8.0 ± 4.6	0	129.2 ± 40.0
AlA (μmol)	0	< 0.5	< 0.5	< 0.5
DFA (μmol)	0	212.6 ± 45.3	0	178.5 ± 55.2
Fe (μmol)	0.1 ± 0.1	8.3 ± 5.5	1.2 ± 1.1	121.2 ± 38.2
Al (μmol)	0.13 ± 0.12	0.29 ± 0.09	0.07 ± 0.05	0.22 ± 0.05
Renal clearance of DFA (ml h^{-1} kg^{-1})		91		85
Renal clearance of FeA ml h^{-1} kg^{-1}		516		1716
6 h urine volume (ml)	324 ± 142	354 ± 160	532 ± 344	743 ± 387

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