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The pharmacokinetics of dexfenfluramine in obese and non-obese subjects

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The pharmacokinetics of dexfenfluramine (d-F) and its metabolite dexnorfenfluramine (d-NF) were compared in 10 obese (145 ± 13 s.d. % of ideal body weight (IBW)) and 10 non-obese healthy volunteers (93 ± 8% IBW). Each group included five men and five women, aged 28 ± 8 years. Subjects were given single doses of d-F i.v. (15.5 mg base infused over 3 h) and orally (25.9 mg base in capsules) on separate occasions. After i.v. infusion in obese subjects, the volume of distribution (V_{ss}) of d-F was significantly higher (969.7 ± 393.3 l; 95% CI 688.6–1250 l) than in controls (668.7 ± 139.6 l; 95% CI 568.9–768.5 l; $P < 0.01$). Clearance was not significantly different (43.9 ± 21.0 l h^{-1} *vs* 37.3 ± 10.6 l h^{-1}) and the terminal half-life tended to be longer (17.8 ± 9.4 *vs* 13.5 ± 3.9 h NS). Combined data from the two groups indicated a positive correlation between V_{ss} and % IBW ($r = 0.544$; $P < 0.02$). The oral bioavailability of d-F was 0.61 ± 0.15 in obese subjects and 0.69 ± 0.11 in controls. There was no significant difference between obese subjects and controls in C_{max}, t_{max} and $t_{1/2,z}$ (C_{max}: 20.1 ± 6.7 and 27.3 ± 6.2 μg l^{-1}; t_{max}: 3.5 *vs* 3.0; $t_{1/2,z}$: 16.5 ± 7.1 *vs* 14.5 ± 2.6 h respectively). The AUC ratio expressed in molar units for d-F/d-NF was 2.29 ± 1.78 (i.v.) *vs* 1.25 ± 0.64 (oral) in obese subjects and 2.05 ± 1.26 (i.v.) *vs* 1.40 ± 0.87 (oral) in controls. Thus d-F has a high clearance with a large tissue distribution in both excess lipid and lean tissues and V_{ss} varies directly and significantly with body weight. The clinical significance of these data is not known.

Keywords dexfenfluramine pharmacokinetics obesity

Introduction

Dexfenfluramine (d-F) has a more specific effect on the serotoninergic system than racemic fenfluramine. It activates central serotoninergic transmission by inhibiting serotonin reuptake into presynaptic neurons and by enhancing its release into brain synapses. d-F also acts peripherally on thermogenesis, lipogenesis, and gastric emptying [1,2]. Because d-F has actions on many aspects of body weight regulation, it is frequently prescribed in the treatment of obesity [3].

Most of the published pharmacokinetic data on d-F refer to oral administration in healthy normal weight volunteers [4–7]. There is no information on its pharmacokinetics in obese patients, although the pathophysiological changes caused by obesity are known to alter the pharmacokinetics of many drugs. The distribution volume of highly lipophilic substances is increased and their elimination half-life is prolonged [8, 9]. In keeping with its high lipid solubility (octanol:buffer partition coefficient of 890 at 37° C) d-F is extensively taken up by all tissues of the body [1]. These data suggest that its pharmacokinetics could be modified in obese patients. We have therefore compared the pharmacokinetics of d-F in obese subjects and healthy non-obese volunteers.

Methods

Subjects

The obese and control subjects were all active adults, aged 29 ± 9 (obese) and 27 ± 6 years (control) (mean ± s.d.). There were five men and five women in each group. All had normal cardiac, respiratory, hepatic and renal function. The plasma triglyceride concentration in the obese patients (1.4 ± 0.5 mmol l^{-1}) differed from that in the controls (0.8 ± 0.2 mmol l^{-1}).

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The weights of all subjects had been stable for at least 2 months before the study and they had not taken any medication, other than oral contraceptives, for 2 weeks before entry. Ideal body weight (IBW) was defined from life insurance tables [10]. The percentage IBW was calculated as the ratio of total body weight to IBW; it was 145.7 ± 13.3 in the obese subjects, 93.2 ± 8.4 in the controls. The body mass index (kg m^{-2}) was 32.2 ± 2.9 in the obese patients group and 20.8 ± 2.0 in controls. Approval for the study was obtained from the Ethics Committee of the Saint-Antoine Hospital and each subject gave written informed consent.

Study design

The study used a cross over design with an intervening 2 week wash-out period. After an overnight fast, each subject remained supine and was given, in random order, either a single oral dose (*D*p.o.) of 30 mg d-F hydrochloride (25.92 mg base) as a capsule (Servier Laboratories), or a single i.v. (*D*i.v.) infusion of d-F hydrochloride solution at a constant rate over 3 h. The mean doses actually infused were 17.63 ± 1.24 mg d-F hydrochloride (15.23 ± 1.07 mg base) in obese subjects, and 18.08 ± 0.96 mg d-F HCl (15.62 ± 0.83 mg base) in controls.

Venous blood samples were collected just before oral drug administration and at the start of the i.v. infusion, and hourly thereafter from 1 to 8 h and at 24, 36, 48, 72 h. This schedule was used to fit in with working practices in the hospital and the quantification limit of the drug assay. All plasma samples were stored at −20° C until assayed.

Drug assay

The plasma concentrations of d-F and of dexnorfenfluramine (d-NF), its de-ethylated active metabolite, were determined by gas chromatography with a capillary column and a nitrogen-specific detector. The limit of accurate determination was 2 ng ml^{-1} [11]. All plasma concentrations are expressed as drug base.

Pharmacokinetic and statistical analysis

Plasma drug concentrations were analyzed by an iterative nonlinear least-squares fitting program without weighting factor [12]. The following pharmacokinetic parameters were determined for the i.v. route: AUC by the trapezoidal method, clearance (CL = dose/AUC), distribution volume at steady state (V_{ss}) and half-life of terminal phase ($t_{1/2,z}$). The parameters for oral administration were in addition to the above, C_{max}, t_{max}, lag time (t_{lag}), and bioavailability:

$$F = \frac{\text{AUCp.o.}}{\text{AUCi.v.}} \times \frac{D\text{i.v.}}{D\text{p.o.}}$$

The area under the concentration-time curve from time zero to the last time at which the metabolite was measurable, AUC(0,*t*), was also determined for d-NF. The AUC(0,*t*) ratio for d-F relative to d-NF was calculated in molar units (μmol l^{-1} h). The molecular weight of base is 231 for d-F and 207 for d-NF.

Comparisons were made using the Mann Whitney U-test.

Results

Table 1 shows the mean values of the pharmacokinetic parameters of dexfenfluramine for obese and control groups. The plasma clearance after i.v. infusion was similar in both groups. The V_{ss} was large and was significantly greater in obese patients (969.7 ± 393.3 l) than in controls (668.7 ± 139.6 l) ($P < 0.01$). The 95% CI of mean values were 688.6–1250.8 l in the obese group and 568.9–768.5 l in controls. The $t_{1/2,z}$ tended to be longer in the obese subjects (mean value 17.8 h) than in controls (13.5 h), but the difference was not statistically significant. When the results of the two groups were combined there was a positive and significant correlation between % IBW and V_{ss} ($r = 0.544$, $P < 0.02$) (Figure 1). There was no difference between the groups when V_{ss} was expressed per kg body weight.

Orally administered d-F appeared rapidly in the blood (lag time = 0.86 ± 0.15 h in controls and 1.42 ± 0.45 h in obese subjects), and C_{max} was reached within about 3 h in both groups. The mean values of CL and $t_{1/2,z}$ were similar to those observed after i.v. infusion. The other parameters were not significantly different in the obese subjects and controls. The mean absolute bioavailability of d-F for the capsules was 61% in obese subjects and 69% in controls.

Pharmacokinetic data for dexnorfenfluramine are shown in Table 1. The mean lag time values were shorter ($P < 0.05$) and the ratios of AUC(0,*t*) for d-F to d-NF were lower ($P < 0.01$) after the oral than the i.v. route. The only parameter that was significantly different in obese subjects and controls was C_{max} after i.v. administration, values being slightly lower in obese subjects ($P < 0.05$).

Discussion

The pharmacokinetic data for dexfenfluramine in normal volunteers obtained in this study, confirm and extend those published for oral and i.v. administration [4–7]. d-F has an extensive distribution volume, as might be expected from its lipophilicity. In the current study the value of $t_{1/2,z}$ is similar to previously published results.

The de-ethylated active metabolite, d-NF, appeared slowly in the plasma but it remained in the circulation much longer. It appears to be more rapidly formed and in greater quantities after oral administration than after i.v. infusion. This suggests that the parent drug is dealkylated during its first pass through the liver. In contrast to data from Debbas *et al.* [7], but in agreement with those of Caccia *et al.* [4, 6] the

Table 1 Mean (± s.d.) pharmacokinetic parameters of dexfenfluramine and dexnorfenfluramine (10 subjects per group)

	i.v. route		*Oral route*	
Parameter	*Obese subjects*	*Control subjects*	*Obese subjects*	*Control subjects*
Dexfenfluramine				
D (mg base)	15.23 ± 1.07	15.62 ± 0.83	25.92 ± 0	25.92 ± 0
AUC(0,t) (μg l^{-1} h)	360.0 ± 171.1	381.6 ± 114.7	372.7 ± 223.7	444.3 ± 131.3
AUC (μg l^{-1} h)	436.4 ± 284.2	448.9 ± 150.0	436.0 ± 249.6	509.9 ± 160.5
CL ($l\ h^{-1}$)	43.9 ± 21.0	37.3 ± 10.6	43.1 ± 21.2	38.3 ± 12.5
V_{ss} (l)	969.7 ± 393.3**	668.7 ± 139.6	1088.0 ± 714.5	808.7 ± 152.2
V_{ss} ($l\ kg^{-1}$)	10.2 ± 3.2	11.3 ± 2.2	11.2 ± 6.2	13.7 ± 2.7
$t_{1/2,z}$ (h)	17.8 ± 9.4	13.5 ± 3.9	16.5 ± 7.1	14.5 ± 2.6
C_{max} (μg l^{-1})			20.1 ± 6.7	27.3 ± 6.2
t_{max} (h)			3.5 (2.0–5.0)[a]	3.0 (2.5–4.0)[a]
F			0.61 ± 0.15	0.69 ± 0.11
Dexnorfenfluramine				
t_{lag} (h)	4.9 ± 1.2	3.9 ± 1.0	1.9 ± 0.4	1.6 ± 0.5
C_{max} (μg l^{-1})	4.5 ± 1.3*	6.0 ± 1.1	7.7 ± 2.1	9.3 ± 2.3
t_{max} (h)	24.0 (23.0–32.0)[a]	23.0 (7.0–32.0)[a]	6.0 (4.6–8.0)[a]	5.0 (3.0–7.0)[a]
AUC(0,t) (μg l^{-1} h)	177.3 ± 75.2	202.9 ± 72.2	293.7 ± 86.1	331.5 ± 96.0
d-F/d-NF (μM l^{-1} h)	2.29 ± 1.78	2.05 ± 1.26	1.25 ± 0.64	1.40 ± 0.87

[a]median (range).
Significantly different from control subjects: *$P < 0.05$; **$P < 0.01$.

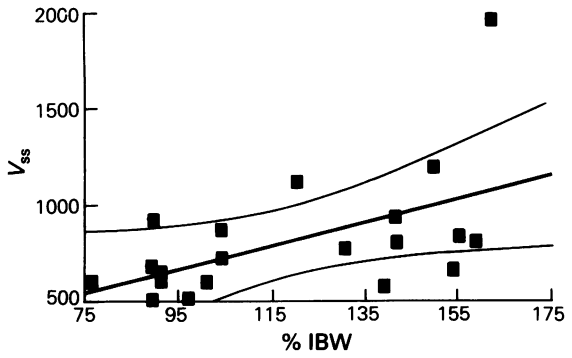

Figure 1 Linear regression (± s.d.) of the apparent volume of distribution (V_{ss} in l) onto percentage of ideal body weight (% IBW) for dexfenfluramine administered by i.v. route. Control subjects: ≤ 110% IBW. Obese subjects: > 110 % IBW. V_{ss} = 6.113% IBW (± 2.2) + 88.5 (± 273), $r = 0.544$; $P < 0.013$.

metabolic ratio d-F/d-NF favoured the parent drug. This ratio varied considerably between subjects (in controls: from 1.0 to 5.22 i.v. and 0.57 to 3.61 p.o.; in obese subjects: 1.18–6.79 i.v. and 0.46–2.03 p.o.). The pharmacokinetic characteristics of d-NF are similar to those of norfenfluramine [13, 14].

The main pharmacokinetic characteristic of d-F in the obese subjects was that its distribution volume was significantly greater after i.v. administration and the $t_{1/2,z}$ tended to be longer. The positive correlation between V_{ss} and % IBW suggests that d-F distributes into the excess body weight. These observations are in keeping with those of Campbell [14] who found that the distribution volume of *rac*-fenfluramine, in a single obese patient, was three times greater than in normal weight patients. Conversely, the distribution volume of d-F divided by the actual body weight (in kg) was not significantly different in the two groups of subjects. This indicates that d-F is distributed equally into the excess fat and lean tissues.

Although the lipophilic nature of d-F would suggest that it is extensively distributed in lipid tissues, the distribution of lipophilic drugs does not always follow this simple rule. For example, some benzodiazepines, such as diazepam and midazolam, have much larger total and weight-corrected distribution volumes in obese patients. Other benzodiazepines (lorazepam) and lignocaine do not diffuse into lipid tissues so much and total V, but not V per kg, is significantly increased [8]. The distribution characteristics of d-F resemble those of the latter drugs. This discrepancy between the lipophilicity of d-F and its restricted distribution in fat tissues could be explained by the extent of its diffusion in all other tissues of the body [1].

The potential clinical relevance of this study relates to the dosage adjustment when obese patients lose weight. In view of the similarities in V corrected for body weight and CL in obese and non-obese subjects, loading dose should be based on total body weight and maintenance dose calculated using the ideal body weight. Nevertheless, the application of these pharmacokinetic principles is limited by uncertainty over the relationship between the plasma con-

centrations of fenfluramine derivatives and their anorectic activity. Blundell & Campbell [15] observed that anorectic potency in rats was best predicted from the sum of fenfluramine and norfenfluramine blood concentrations and that the prolonged duration of effect is mediated by the active metabolite. There was a significant correlation between the reduction in hunger rating and concentrations of d-F after a single dose in healthy human volunteers. Some clinical trials in obese patients have shown a significant correlation between the plasma concentrations of fenfluramine and its metabolite and weight loss, while in others it was concluded that plasma concentrations were only poor predictors of weight loss, accounting for only about 15–18% of the variance [16, 17].

In conclusion, the extensive tissue distribution of dexfenfluramine results in a total distribution volume that is greater in obese patients than in lean subjects. However, its distribution seems to be as great in lean tissues as in lipid tissues. The therapeutic application of these pharmacokinetic data awaits a better understanding of the relationship between plasma drug concentrations and activity.

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