The pharmacokinetics of methadone in healthy subjects and opiate users

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Aims There is some evidence that monitoring methadone plasma concentration may be of benefit in dosage adjustment during methadone maintenance therapy for heroin (opiate) dependence. However, the kinetics of oral methadone are incompletely characterized. We attempted to describe the latter using a population approach combining intensive 57 h sampling data from healthy subjects with less intensive sparse 24 h data from opiate users.

Methods Single oral doses of *rac*-methadone were given to 13 drug-naive healthy subjects (7 men and 6 women) and 17 opiate users beginning methadone maintenance therapy (13 men and 4 women). Plasma methadone concentrations were measured by h.p.l.c. Kinetic analysis was performed using the P-Pharm software.

Results Comparison of kinetic models incorporating mono- or biexponential disposition functions indicated that the latter best represented the data. The improvement was statistically significant for the data from healthy subjects whether the full 57 h or truncated 24 h profiles were used ($P<0.031$ and $P<0.024$, respectively), while it was of borderline significance for the more variable data from opiate users ($P=0.057$) or for pooled (healthy subjects and opiate users) data ($P=0.066$). The population mean oral clearance of methadone was 6.9 ± 1.5 s.d. $1\,h^{-1}$ (5.3 ± 1.2 s.d. $1\,h^{-1}$ using 0–24 h data) in the healthy subjects. The results of separate analyses of the data from opiate users and healthy subjects were in contrast with those obtained from pooled data analysis. The former indicated a significantly lower clearance for opiate users (3.2 ± 0.3 s.d. $1\,h^{-1}$, $P<0.001$); 95% CI for the difference $=-3$ to $-6\ 1\,h^{-1}$ and no difference in the population mean values of V/F (212 ± 27 s.d. l and 239 ± 121 s.d. l, $P=0.15$), while according to the latter analysis addiction was a covariate for V/F but not for oral clearance. A slower absorption of methadone in opiate users was indicated from the analysis of both pooled and separate data. The median elimination half-life of methadone in healthy subjects was 33–46 h depending on the method used to calculate this parameter.

Conclusions Estimates of the long terminal elimination half-life of methadone (33–46 h in healthy subjects and, possibly, longer in opiate users) indicated that accurate measurement of this parameter requires a duration of sampling longer than that used in this study. Our analysis also suggested that parameters describing plasma concentrations of methadone after a single oral dose in healthy subjects may not be used for predicting and adjusting dosage in opiate users receiving methadone maintenance therapy unless coupled with feedback concentration monitoring techniques (for example Bayesian forecasting).

Keywords: methadone, pharmacokinetics, opiate-dependence, population kinetics

Introduction

Methadone has long been the drug of choice for the treatment of patients dependent upon heroin and other narcotics. However, after nearly 50 years of therapeutic use, details of the kinetics of this drug remain incomplete. Clinicians still have very limited knowledge of the most appropriate method for titrating the dose of methadone to an equivalent dose of heroin, and of the most suitable dosage interval [1]. Systematic investigation of dosage requirements in methadone maintenance therapy is a relatively recent development [2].

Another justification for a better understanding of methadone kinetics relates to the optimization of the duration of administration of naltrexone for the treatment of methadone overdose [3–5].

Early studies indicated wide variability in the plasma concentration-response relationship of methadone [6], thereby casting doubt on the value of monitoring plasma

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methadone. In contrast, more recent findings suggest that such monitoring may be useful in guiding dosage [7–13]. Furthermore, controlled studies in monkeys indicate that the reinforcing effect of methadone does vary in relation to plasma drug concentration [14].

In general, there have been few attempts to characterize the kinetics of methadone in opiate users, and to use this information in the development of rational dosage regimens [15]. This may reflect the difficulty of obtaining blood samples owing to poor venous access, the unreliability of these patients and their inability or unwillingness to remain on studies for more than 24 h [10]. More comprehensive data on methadone kinetics have been collected from other clinical groups including cancer patients receiving i.v. infusions of methadone (5–40 mg) for the relief of chronic pain [16–20], and surgical patients given parenteral methadone for peri-operative analgesia [21, 22] (Table 1). Nevertheless, in two thirds of these studies, blood samples were collected for only 24 h and in the others for no longer than 48 h (Table 1). Thus, limitations on sampling time have generated significant disagreement about the kinetics of methadone, particularly in relation to the number of exponential terms required to describe its disposition and to estimates of its terminal elimination half-life. While some investigators have used two [18, 24–27] or three exponentials [20], others have indicated that a single exponential function was adequate [15, 28–30]. In addition, data from these studies cannot necessarily be extrapolated to opiate-dependent patients receiving long-term substitution therapy with much higher doses of oral methadone [21].

The published kinetic studies on methadone indicate that it has a terminal half-life of between 15 h and 55 h. However, calculation of the ratio of the sampling to the reported half-life (Table 1) clearly indicates that the duration of sampling has been insufficient to recover most of the AUC. Assuming a terminal half-life of 24 h, it would be expected that sampling over about 60 h would recover more than 80% of the AUC, thereby allowing an accurate description of methadone kinetics. Therefore, the aims of this study were to provide an improved characterization of the kinetics of methadone after a single oral dose. However, since it was not possible to obtain reliable samples over more than 24 h from out-patient opiate users, 24 h data from these individuals were combined with data from intensive 57 h sampling in healthy subjects in the hope that this would provide accurate estimates of the population kinetics of the drug and relevant covariables. These estimates might then be used as a first step in the development of a Bayesian forecasting approach to predict and adjust methadone dosage and compliance in opiate-dependent patients.

Methods

Subjects

Thirteen healthy subjects (7 male, 6 female; median age 24 (range 21–45) years; median weight 69 (range 54–81) kg) and 17 opiate users (13 male, 4 female; median age 25 (range 17–36) years; median weight 65 (51–95) kg) were studied. None of the healthy subjects had ever taken methadone; two smoked cigarettes (15 per day); and the median alcohol consumption of the group was 12 (range 0–40) units/week. The opiate users were about to begin a programme of methadone treatment at the Leeds Addiction Unit. All were dependent upon heroin for periods of between 1–6 years, and had not taken methadone during the previous 6 months. All but one smoked cigarettes (median 20 (range 0–40) per day) and 5 consumed alcohol on a regular basis (range 0–40) units/week). The results of routine clinical laboratory tests were within normal limits in both healthy subjects and opiate users, and all subjects gave informed consent to take part in the study, which was approved by the local ethics committee.

Drug administration

The healthy subjects received a single oral dose of *rac*-methadone HCl (mean 13 ± 3 s.d. mg; range 8–15 mg) as Drug Tariff Formula (DTF) mixture. The opiate users were examined and monitored for signs of opiate withdrawal using the Symptom Severity Assessment (SSA) chart [31] before commencing methadone treatment. Their mean initial dose of *rac*-methadone was 39 ± 17 s.d. mg (range 15–80 mg), given as DTF mixture. After witnessed oral consumption, the container was rinsed and the rinse swallowed. All subjects were asked to rinse their mouths and swallow, to ensure that all of the dose had been taken.

Sample collection

A pre-dose blood sample (10 ml) was drawn by venepuncture into heparinized Monovette blood collection tubes (Sarsted, Leicester). Further blood samples (10 ml) were taken through a butterfly cannula placed in a forearm vein at 1 h intervals for the first 5 h and at longer intervals until 24–27 h in all subjects (9–10 samples in healthy volunteers and 6–10 samples in opiate users, respectively). Additional samples were taken at 31, 36, 49 and 57 h in the healthy subjects. After centrifugation of the blood for 5 min (1000 *g*) plasma was transferred to polypropylene tubes and stored at -20° C until assay. Pre-dose urine samples (20 ml) were also collected and their pH measured. The urine was then screened for common drugs of abuse including opiates, cocaine, cannabinoids, benzodiazepines and amphetamines by automated enzyme immunoassay (EMIT, Syva, Berkshire).

Analytical methods

Plasma (2.0 ml), together with 0.5 ml of a solution of benzhexol (internal standard, 1 mg l^{-1}) in aqueous methanol (50 : 50 v/v) and 0.5 ml of sodium bicarbonate buffer (1 M, pH 10) was extracted twice with *n*-butyl chloride (5.0 ml) saturated with water, followed by centrifugation at 4° C for 7 min (1000 *g*). The organic layer was aspirated and evaporated at 50° C in a Model GV2 refrigerated solvent trap and centrifugal evaporator (Uniscience, London). The residue was dissolved in 0.2 ml of methanol and stored at -20° C pending chromatography. Concentrations of methadone were assayed achirally by normal phase h.p.l.c. using

Table 1 Pharmacokinetic parameters for methadone from the literature (mean ± s.d.).

Population	*Dosage*	*Number of exponential terms in decay phase*	*Sampling period*	$t_{1/2,\,z}$ (h)	*CL* ($l\,h^{-1}$)	V ($l\,kg^{-1}$)	*Reference*
Healthy subjects (6F)	Single oral	1	2–48 h	19			[30]
Healthy subjects (5M)	Single oral	1	4–24 h	15 ± 4			[29]
Healthy subjects (6, 6, 4, M)	Single oral	1	peak-48	22 (R: 25; S: 24)			[34]
Patients with chronic pain (3M, 5F)	Single oral/i.v.	3	48 h	23	6.4	3.6 ± 1.2†	[20]
Patients with chronic pain (76M, 109F)	i.v. infusion	2	30 h post-inf.	32	11.2		[18]
Patients with chronic pain (5M, 2F)	Single oral/i.v.	2	48 h	38 (R)	R: 9.5	R: 497 (l)†	[37]
				29 (S)	S: 7.7	S: 289 (l)†	
Post burn patients (14)	Variable infusion	NS	24 h	2.6 ± 1.1	53 ± 19	180 ± 68 (l)	[46]
Addicts (12M)	Single oral	2	4–27 h	55 ± 27			[36]
	Oral at SS‡	2	4–24 h	22 ± 7			[36]
Addicts (5M)	Oral at SS	1	4–24 h	25 ± 13			[47]
Addicts (7M, 1F)	Single oral	2	48 h	28 ± 11		2.2 ± 0.4	[24]
Addicts (11M, 1F)	Single oral	2	NS-48 h	35 ± 12		3.8 ± 0.6	[25]
	Oral at SS	2	NS-48 h	34 ± 7		4.7 ± 1.0	[25]
Addicts (6M,1F)	Pulse of oral/i.v.						
	d3-Methadone and	1	8–24 h	22 ± 2			[28]
	methadone at SS	1	8–24 h	52 ± 20			[28]
Addicts with therapeutic failure (7M, 1F)	Pulse of i.v.						
	d3-Methadone	1/2	NS-24 h	25 ± 3	6.2 ± 2.2	1.4 ± 0.3	[26]
Addicts (unselected; 11M, 1F)	at SS	1/2	NS-24 h	34 ± 7	6.7 ± 2.2	2.7 ± 0.4	[26]
Addicts (11M, 9F)	Oral at SS	2	24 h	31	6.9 ($l\,h^{-1}$ $70kg^{-1}$)§	2.2	[27]
Addicts (2M,3F)	Oral at SS	1	NS-24 h	27	4.2 ($l\,h^{-1}$ $70kg^{-1}$)§	6.7	[15]

†V_{area}; NS = Not stated; ‡Steady-state; §oral clearance.

an Apex-1 silica column (25 cm × 0.46 cm i.d.; 5 μ particles) (Jones Chromatography, Llambradach). The retention times of benzhexol and methadone were 5.5 and 6.5 min, respectively [10]. The sensitivity of the assay (signal-to-noise ratio ° 3) was 5 ng ml^{-1}. The between- and within-day coefficients of variation of the assay at a methadone concentration of 100 ng ml^{-1} and 5 ng ml^{-1} were 9.5% and 3.5% (9.8% and 7.2%), respectively ($n = 10$).

Data analysis

The time-course of plasma methadone concentration was described by both mono- and biexponential disposition functions with first-order input using the P-Pharm software package (Version 1.3e, SIMED, Creteil, France). The two models were compared using the Akaike Information Criterion (AIC) [32], the *F*-test, and by examination of residuals.

Data from healthy subjects and opiate users were analysed separately and again after pooling the data. A separate kinetic analysis was carried out on truncated (24 h) data from the healthy subjects and the results were compared with the 0–24/27 h data from the opiate users. When analysing pooled data, addiction was introduced as a covariable and its influence on kinetic parameters was investigated by stepwise multiple regression.

In all of the above analyses a heteroscedastic (1/[concentration]^2) distribution of error around the data was assumed. Oral clearance (CL/*F*), central volume of distribution (V/F), the transfer rate constants between central and peripheral compartments (k_{12}, k_{21}), the apparent absorption rate constant (ka) and lag time (t_{lag}) were considered as primary parameters with normal distributions. Thus, a *population mean* and an estimate of its variability could be obtained for each of these parameters.

The terminal elimination half-life ($t_{1/2,\,z}$) and volume of distribution at steady-state (V_{ss}/F) were considered to be secondary parameters in these analyses and *population mean* values (with no measure of variability) were calculated using the following equations:

$$t_{1/2,\,z} = \frac{ln\ 2}{\lambda_z} \qquad \text{(Eq. 1)}$$

$$\lambda_z = 0.5 \times \left[\left(k_{12} + k_{21} + \frac{CL}{V} \right) - \sqrt{\left(k_{12} + k_{21} + \frac{CL}{V} \right)^2 - 4 \times k_{21} \times \frac{CL}{V}} \right] \qquad \text{(Eq. 2)}$$

$$V_{SS}/F = V/F \times \left(1 + \frac{k_{12}}{k_{21}} \right) \qquad \text{(Eq. 3)}$$

Assuming no covariation between the components of $t_{1/2,\,z}$ and V_{ss}/F, a measure of the variance of these *population means* was calculated using the following approximation [33]:

$$\text{var}(y) \approx \sum_{i=1}^{n} \left[\left(\frac{\partial y}{\partial x_i} \right)^2 \times \text{var}(x_i) \right] \qquad \text{(Eq. 4)}$$

Where y is the dependent variable and, $x_1, \ldots\ldots\ldots\ldots, x_n$ *are the independent variables and* $\partial y/\partial x_i$ is the partial derivative of y with respect to x_i. Two further approaches were used to estimate the population elimination half-life in the healthy subjects. Firstly, a value was calculated using individual estimates of half-life. The latter were obtained using Equations 1 and 2 and individual values of the relevant primary kinetic parameters (CL/*F*, V/F, k_{12}, k_{21}) provided from a maximum *a posteriori* probability (MAP) Bayesian fitting procedure. This method provided two population estimates depending upon the assumption of a normal or a log-normal distribution for elimination half-life.

Secondly, the population analysis was re-run with $t_{1/2,\,z}$ as a primary parameter with a log normal distribution.

Population mean values of CL/*F* and V/F in the two groups were compared statistically using the Z-test. The differences between CL/*F* and V/F calculated from 57 h and 24 h data from the healthy subjects were also evaluated using this test. The model independent parameters C_{max} and t_{max} were noted directly from the data. The former were compared in the two groups using Student's *t*-test and the latter were compared using Wilcoxon's Rank Sum Test.

Finally, the relatively rich data set from the healthy subjects was analysed by conventional curve fitting to the plasma drug concentration time from each individual subject (possible in 10 of the 13 subjects). Initial parameter values for iteration were provided from the population estimates. The results of these analyses were used to evaluate the accuracy of parameter estimates obtained by fitting the population data. It was not possible to fit individual data from opiate users by conventional analysis since the data were too sparse.

Results

Adverse drug effects

The first four healthy subjects to be studied experienced nausea, vomiting and light-headedness after the administration of methadone. Therefore, the methadone dose was decreased in the other members of this group. Nevertheless, all of the healthy subjects experienced some degree of light-headedness, starting 1–3 h after dosing and lasting for about 1 h. All but one healthy subject felt sleepy, 3 slept (2–5 h after dosage), and one reported tiredness at 30 h after receiving methadone. Eight of the 13 healthy subjects experienced nausea, and 2 men and 3 women vomited on one or more occasions. Some subjects also had headaches and felt thirsty. These effects occurred between 7–24 h and 15–50 h after dosage, respectively.

Four of the 17 opiate users reported adverse effects after methadone dosage. Two felt sleepy and two felt nauseated and vomited.

Urine drug screening

Pre-dose urine samples from all of the healthy subjects were free of opiates. Cannabinoids were detected in the urine of one subject. All 17 opiate users had opiate-type drugs in their pre-dose urine sample. In addition, 12 of the opiate

users had benzodiazepines, cannabinoids, amphetamines or cocaine in their urine.

Pharmacokinetics

Plasma methadone concentrations in the healthy subjects and opiate users are shown in Figure 1a and 1b, respectively. The data from the latter group were clearly more variable.

Population mean fits of the models incorporating mono- and biexponential disposition functions to data from the healthy subjects are shown in Figure 2a, and 2b; the data were normalized for a 10 mg dose. Residuals for each of these models are shown in Figure 2c and d, respectively. Corresponding pharmacokinetic parameters are listed in Table 2. The AIC value decreased from 3.20 to 3.05 when using a biexponential compared with a monoexponential disposition function. The better fit of the biexponential function to the population data was confirmed by the *F*-test ($F=32.4$; $P<0.031$), and the residual plots indicated systematic deviation of the monoexponential model from the data (Figure 2c, d). The population mean value of oral clearance was 16% higher based on the mono- compared with the biexponential model ($P<0.02$) and the terminal elimination half-life was 40% shorter (Table 2). Significant improvement of the fits incorporating biexponential disposition was also observed for 24 h truncated data from healthy subjects ($P<0.024$).

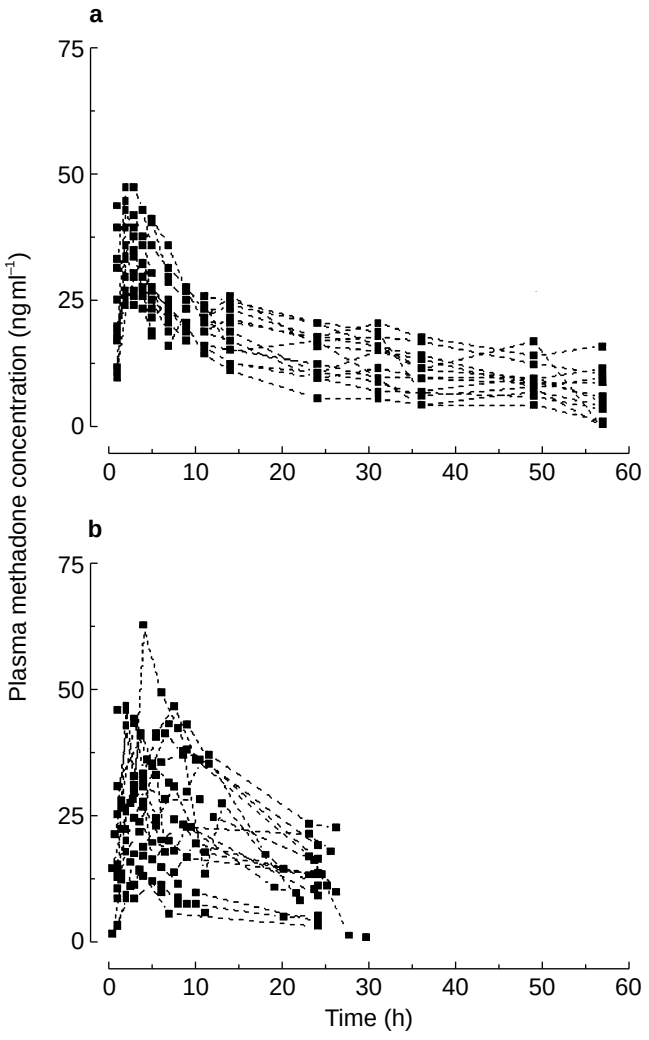

Figure 1 Plasma methadone concentrations (ng base ml^{-1}) in a) 13 healthy subjects and b) 17 opiate users after oral administration of a single dose of methadone HCl (data are normalized for a 10 mg dose of methadone HCl).

Population mean fits of the two models to data from the opiate users are shown in Figure 3a, b; the data were normalized for a 10 mg dose. Residuals for each of these models are shown in Figure 3c and d, respectively. The distinction between the mono- and biexponential models was not as clear as in the case of the data from healthy subjects. The AIC showed a decrease from 4.80 to 4.74 in favour of biexponential disposition, while the significance of improvement in fits according to the *F*-test was borderline ($F=16.9$; $P=0.057$) and the residual plots did not reveal systematic deviations using either function (Figure 3c, d).

An examination of possible co-variables (weight, age, sex, smoking, alcohol consumption, urine pH, concomitant drugs) showed no significant relationship to CL/F or V/F in healthy subjects. In opiate users weight was positively related to V/F and explained 34% of its variance.

Based on the biexponential model, the population mean value of CL/F was significantly lower in opiate users (3.2 l h^{-1}) than in healthy subjects, irrespective of whether full (57 h) or truncated (24 h) data from the healthy subjects were examined (6.9 and 5.3 l h^{-1}, respectively) (Table 2). A high variance (>50% CV) in V/F was observed in opiate users, but no difference in the mean value was detected relative to that in healthy subjects (Table 2). However, the *population mean* V_{ss}/F value, as calculated from the micro-constants of the model, was double that in healthy subjects (870 *vs* 376 l or 422 l using 24 h data) (Table 2), suggesting a possible difference in the extent of distribution of methadone in opiate users.

The opiate users had a longer apparent absorption half-life compared with healthy volunteers (1.1 *vs* 0.25 h, $P<0.001$; Table 3). In addition, the median value of t_{max} was twice that in opiate users although the difference was not statistically significant ($P=0.68$). The mean value of C_{max} was similar in the two groups although it was twice as variable in the opiate users (Table 3).

Analysis of pooled data gave population mean CL/F and V/F values similar to those obtained by separate analysis of data from opiate users (Table 2) but different from those obtained from separate analysis of data from healthy subjects. However, when *a posteriori* values of CL/F in healthy subjects from pooled data analysis were compared with corresponding values obtained by conventional data analysis for these individuals, it was clear that the population model based on pooled data underestimated drug clearance in healthy subjects by about 50% (Figure 4). Separate population analysis of healthy subject data provided *a posteriori* values of clearance that were in agreement with those obtained using conventional analysis (Figure 4).

Inconsistent values of the population $t_{1/2,\,z}$ in healthy subjects were obtained by different methods (Figure 5). The population $t_{1/2,\,z}$ in opiate users (as calculated by the first approach described in **Methods**) was 207 h, which is much longer than the value estimated in healthy subjects (Table 2). However, the estimate of variability for this value was very high (±185 h), possibly as a consequence of the relatively short sampling period.

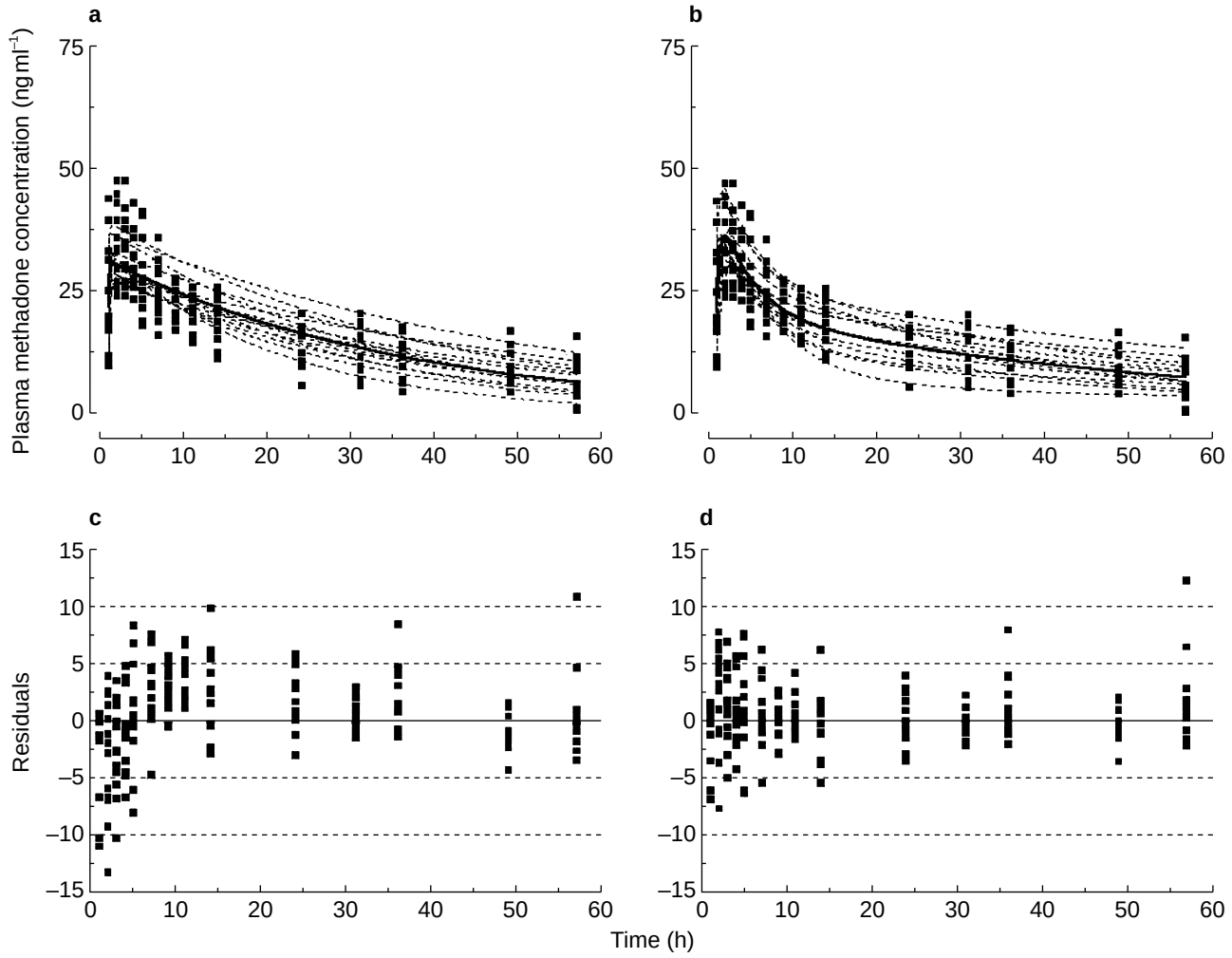

Figure 2 Individual (thin lines) and population mean (thick line) model fits to plasma methadone concentrations (data points, ng base ml^{-1}) after oral administration of a single dose of methadone HCl to 13 healthy subjects (data are normalized for a 10 mg dose of methadone HCl) a) first-order input with mono-exponential disposition, b) first-order input with bi-exponential disposition, c) residual plot for (a) and d) residual plot for (b).

Discussion

Despite the administration of a very low oral dose of methadone the healthy volunteers experienced a high incidence of nausea and vomiting. This was surprising as others have not reported such a finding [34].

The primary aim of the pharmacokinetic analysis was to determine whether single dose data on methadone obtained by intensive and extended sampling in healthy subjects might form a basis for predicting dosage requirements and assessing poor compliance in opiate users using a limited sampling strategy. This involved a comparison of alternative pharmacokinetic models, and a comparison of data obtained in healthy subjects with more limited single dose data from opiate users commencing methadone maintenance treatment.

With regard to the choice of pharmacokinetic model, analysis of the data from the healthy subjects supported previous studies [18, 24–27, 36, 37] advocating the use of a biexponential rather than a monoexponential disposition function. However, a clear improvement of fit using the biexponential function could not be demonstrated with the variable, sparse and more limited 24 h data obtained in the opiate users. Nevertheless, it seems prudent to assume that the biexponential model should apply to both healthy subjects and opiate users. Based upon the kinetic analysis of the data from healthy subjects, we estimate that about 20% of the total AUC measured in the opiate users would reside in the distribution phase. Thus, a significant overestimation of oral clearance would be expected when sampling is limited to only 24 h (i.e. about 4 × the distribution half-life) and a monoexponential function is applied.

Estimates of the mean terminal elimination half-life of methadone in the published literature vary from 15 h to 55 h based on sampling up to 24 h—48 h, with estimates in healthy subjects being less than 24 h (Table 1). It was on this basis that we decided to sample for 57 h in healthy volunteers, with the expectation that at least 80% of the AUC would be captured. However, in retrospect, this proved to be inadequate as our estimates of half-life were longer than 24 h (33–46 h). Our analysis also suggests that the terminal half-life in opiate users may be further prolonged compared with that in healthy subjects. Thus, further studies involving more prolonged sampling remain necessary to characterize the residence of methadone in the body. This issue has considerable clinical significance with regard to detoxification using opiate antagonists with shorter elimination half-lives than methadone.

Table 2 Comparison of population mean pharmacokinetic parameters describing the kinetics of methadone after a single oral dose to healthy subjects and opiate users (mean ± s.d.).

Population (n)	Duration of plasma sampling (h)	Mono-exponential disposition				Bi-exponential disposition					
		CL/F ($l\,h^{-1}$)	V/F (l)	$t_{1/2}$ (h)	$t_{1/2}$abs (h)	t_{lag} (h)	CL/F ($l\,h^{-1}$)	V/F (l)	V_{ss}/F (l)	$t_{1/2,\lambda 1}$ (h)	$t_{1/2,z}$ (h)	$t_{1/2}$abs (h)
Healthy subjects (13)	0–57	8.0 ± 2.5	285 ± 39	24.6 ± 5.0°	0.07	0.9 ± 0.1	6.9 ± 1.5*‡	212 ± 27‡	376 ± 48°	3.0	41 ± 21°	0.25
Healthy subjects (13)	0–24	11.4 ± 3.8	265 ± 42	16.1 ± 3.9°	0.02	1.0 ± 0.0	5.3 ± 1.2‡	222 ± 40†	422 ± 73°	3.2	58 ± 77°	0.22
Opiate users (17)	0–24/27	11.0 ± 2.6	309 ± 190	19.4 ± 17.7°	0.73	0.3 ± 0.3	3.2 ± 0.3§‡	239 ± 121	870 ± 444°	5.8	207 ± 185°	1.1
Pooled data (30)	0–57	8.6 ± 2.8	317 ± 140	25.7 ± 17.0°	0.07	0.9 ± 0.1	3.2 ± 0.8	247 ± 73	719 ± 201°	6.6	159 ± 121	1.4

Significantly different from the value obtained from 0–24 h sampling ($P < 0.002$); ‡Significantly different from value obtained using the mono-exponential model ($P < 0.001$); °An approximation of s.d. is given (see Methods); †Significantly different from the value obtained using the mono-exponential model ($P < 0.005$); §Significantly different from the value obtained in healthy subjects ($P < 0.001$).

Assuming the biexponential model for both healthy subjects and opiate users, our analysis indicates a lower oral clearance in the latter, in agreement with a previous observation of Olsen *et al.* [38], using two healthy male volunteers. Assuming equal bioavailability, the initial distribution of methadone was more variable in opiate users (CV > 50%) compared with healthy subjects (CV < 20%), and the extent of distribution at steady-state may be much greater, although confidence in the value of V_{ss}/F in opiate users is low. Analysis of co-variables that might explain pharmacokinetic variability indicated no support for previous suggestions that oral clearance is affected significantly by sex [27], weight [18] or urine pH [25, 39, 40]. However, weight was indicated as contributing to the variance of V/F in opiate users but, not in healthy subjects.

A study in opiate-tolerant rats [41] has shown that enforced abstinence is associated with an increase in α_1-acid glycoprotein, a major binding site for methadone in plasma [39]. Furthermore, opiate users about to begin a programme of methadone treatment are reported to have elevated plasma concentrations of this protein (1.22 ± 0.10 s.d. mg ml^{-1} *vs* 0.69 ± 0.06 s.d. mg ml^{-1} in controls) [43]. Accordingly, an increase in the plasma binding of methadone in opiate users relative to healthy subjects could explain a relatively low clearance based on total plasma drug concentration. However, although greater variability in plasma α_1-acid glycoprotein concentration might contribute to increased variability in the volume of distribution of methadone in opiate users, based upon measurement of total plasma drug concentrations, it would not be consistent with the apparent increase in the steady-state volume of distribution (V_{ss}/F).

A slower absorption of methadone in opiate users compared with healthy subjects, as indicated by a slower apparent absorption half-life, may reflect the pharmacological effect of opiates in slowing gastric emptying [44].

A general problem highlighted by this study was the difficulty of using a relatively rich data set (from healthy subjects) to augment the analysis of sparse data from a target population (opiate users), when samples from the two populations were not balanced with respect to sampling duration. Thus, the pooled population analysis clearly forced artificially low clearance values on the healthy subjects, which were not substantiated by either separate population or conventional analysis of the healthy subject data. Application of population pharmacokinetics to unbalanced data from different sub-groups should be applied with caution. For example, Hussein *et al.* [45] recently compared the kinetics of proguanil in individuals from five different countries, but the samples used to characterise the kinetic model were only obtained from one of these groups.

For the reasons given above, the results of the separate analyses of the data from the two groups in our study were considered to be more reliable than those obtained from the analysis of pooled data. However, regardless of the approach to data analysis, our findings provide no support for using parameters describing plasma concentrations of methadone after a single oral dose in healthy subjects as a basis for predicting and adjusting dosage in opiate users receiving maintenance therapy. Thus, the present data suggest that there could be appreciable changes in the handling of the

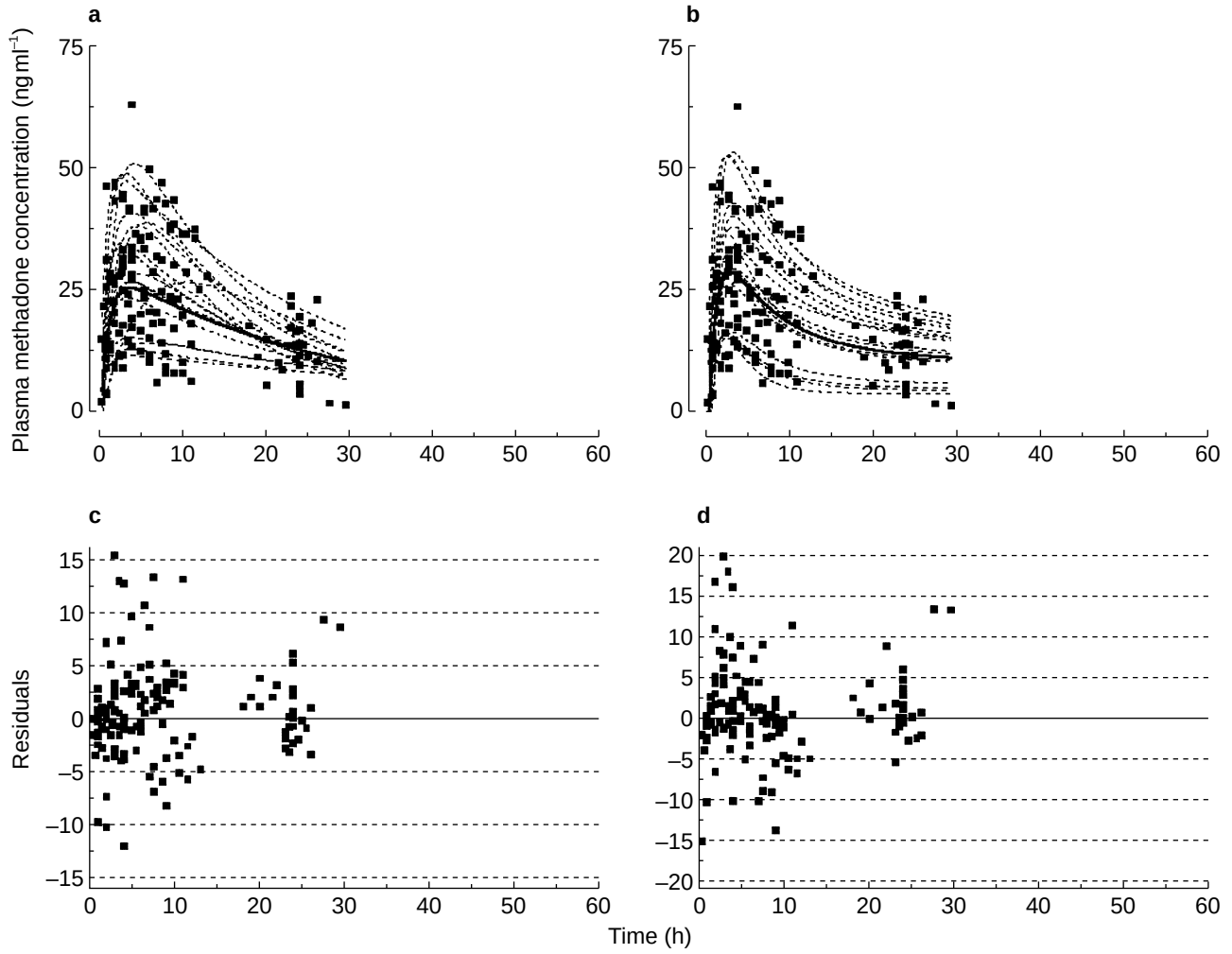

Figure 3 Individual (thin lines) and population mean (thick line); model fits to plasma methadone concentrations (data points, ng base ml^{-1}) after oral administration of a single dose of methadone HCl to 17 opiate addicts about to commence a programme of methadone treatment (data are normalized for a 10 mg dose of methadone HCl). a) first-order input with mono-exponential disposition, b) first-order input with bi-exponential disposition, c) residual plot for (a) and d) residual plot for (b).

Table 3 Model independent pharmacokinetic parameters of methadone after a single oral dose to healthy volunteers and opiate users.

	C_{max} *(mean ± s.d.)* *(ng ml^{-1})*	t_{max} *(median, range)* *(h)*
Volunteers	39.8 ± 8.0	2 (1–4)
Opiate users	37.0 ± 15.6	3.75 (1–7.5)

drug as a consequence of previous drug abuse, at least at the start of methadone therapy.

Because of the imbalance in the duration of sampling in opiate users in comparison with healthy subjects, further studies with more prolonged sampling are needed to substantiate or refute these differences. However, such studies in opiate users could present considerable logistical difficulties in an out-patient setting. As a compromise, it may still be possible, providing that the biexponential model is assumed for opiate users, to use the mean population values from healthy subjects as initial estimates in feedback forecasting methods. Further investigations should also be aimed at clarifying the roles of plasma binding and enantioselective kinetics [48], and the influence of auto-

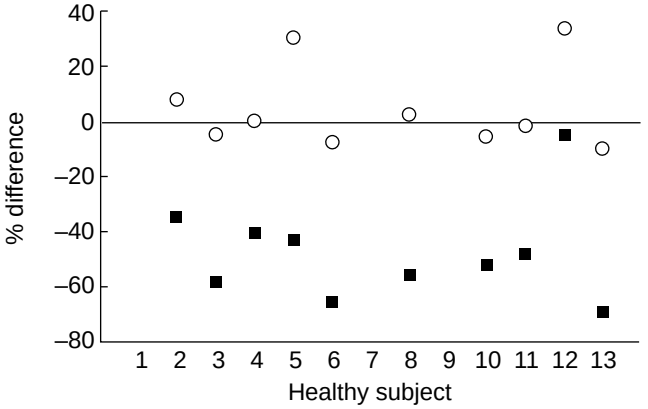

Figure 4 Percentage differences in individual estimates of methadone clearance in healthy subjects derived from separate population fitting of data from healthy subjects (open circles) and population fitting to pooled data (closed squares) both with respect to individual clearances assessed by conventional fitting to individual data points (data from subjects 1, 7 and 9 could not be fitted by the latter method).

enzyme induction and other adaptive changes on the metabolism of methadone [25, 28, 36, 49, 50]. Whether these complexities present formidable obstacles to the

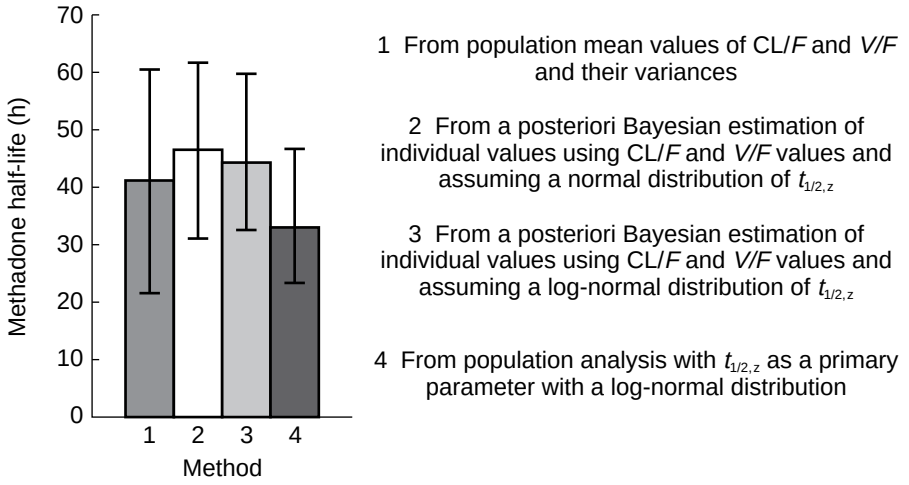

Figure 5 Comparison of population median (±s.d.) estimates of the terminal elimination half-life of methadone in healthy subjects derived by different methods of data analysis.

development of predictive models of methadone kinetics in patients undergoing substitution therapy remains to be seen.

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