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Single Dose Pharmacokinetics and Bioavailability of Methadone in Man Studied with a Stable Isotope Method

U. Meresaar[2], M.-I. Nilsson[1,3], J. Holmstrand[1], and E. Änggård[1,4]

[1]Psychiatric Research Center and [2]Hospital Pharmacy, Ulleråker Hospital, [3]Department of Inorganic and Physical Pharmacy, University of Uppsala, Uppsala, and [4]Department of Alcohol and Drug Addiction Research, Karolinska Institutet, Stockholm, Sweden

Summary. The disposition of methadone was studied in eight opiate dependent subjects during detoxification. Plasma concentrations were determined by mass fragmentography for 48 hours after administration of methadone 20 mg as tablets and simultaneous intravenous injection of deuterium-labelled methadone 20 mg. Pharmacokinetic parameters were calculated for the intravenous dose assuming a two compartment open model. Bioavailability was determined by comparing the areas under the plasma concentration versus time curves of unlabelled and labelled methadone. The beta-phase plasma half-lives varied five-fold, with a range from 8.5 to 47 h. The apparent volumes of distribution varied from 2.1 to 5.6 l/kg. Five patients had a bioavailability exceeding 90%, and three had lower bioavailabilities of between 41 and 76%. The unlabelled and labelled drug appeared to be pharmacokinetically equivalent. The data show that for a majority of these subjects the bioavailability was higher than 45%, the previously reported value. The marked individual variation in methadone pharmacodynamics and kinetics, and the possibilities both of cellular and methabolic tolerance, require an individually optimized dosage regimen.

Key words: methadone; bioavailability, pharmacokinetics, single dose, stable isotope technique, two compartment model

Although methadone has been used as a narcotic analgesic since the second World War, and in the maintenance treatment of opiate addicts for more than 15 years, no formal study of its bioavailability has been reported. Beaver et al. [1] found that methadone given orally to cancer patients was about 45% as effective as an analgesic as the same dose injected intramuscularly.

In the present study we have determined the absolute bioavailability of methadone using a new technique. Following intravenous injection of deuterium-labelled methadone simultaneously with an oral dose of unlabelled drug, the plasma concentrations of the two types of methadone were determined by mass fragmentography. The technique permits precise determination of bioavailability on one occasion in a single patient.

In these experiments it was also possible to determine the pharmacokinetic parameters of methadone according to a two compartment open model following a single intravenous dose.

Material and Methods

Subjects

Eight opiate abusers, admitted to hospital for detoxification, volunteered to participate in the study. Six were applicants for the methadone maintenance

Table 1. Details of the Patients

Subjects	Age [years]	Sex	Weight [kg]
1	22	Male	60
2	22	Male	70
3	21	Female	56
4	27	Male	63
5	29	Male	76
6	26	Male	79
7	25	Male	77
8	26	Male	70

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treatment programme of the hospital. Subjects tolerant to opiates were required, since the dose of methadone given was as high as 40 mg. The age, sex and weight of the patients are given in Table 1. All of them were smokers.

All patients were subjected to physical examination, including clinical blood and urine analysis. Patients 3 and 4 (Table 1) showed moderately elevated values of both serum transaminases (S-ALT, S-AST), and Patient 4 also of alkaline phosphatase. Patients 7 and 8 had elevated serum alanine aminotransferase (S-ALT).

Drug Administration

Food was withheld for eight hours before and four hours after dosing (at 8.00 a. m.). Subsequently, ordinary hospital food was offered. Plenty of fluid was given throughout.

The oral dose was administered as two 10 mg tablets[1] of d,l-methadone hydrochloride (methadone-d_0) together with water 100 ml. Simultaneously, the same amount of d,l-2-dimethylamino-4-4-diphenyl-7,7,7-trideutero-5-heptanone hydrochloride (methadone-d_3) in 5 ml isotonic saline was given as a bolus intravenous injection. The methadone-d_3 was supplied by courtesy of Dr. R. E. McMahon, Eli Lilly Research Laboratories, Indiana, USA. It contained less than 1% of unlabelled methadone according to mass fragmentographic analysis.

Blood Sampling

Blood 10 ml was collected from an indwelling cannula in the best available vein before drug administration and after 0.33, 0.66, 1, 2, 4, 6, 8, 12, 24, 36 and 48 h. The samples were taken into heparinized Vacutainer tubes and immediately centrifuged. The plasma was stored frozen at −20 °C until analyzed.

Determination of Methadone

The plasma concentrations of methadone-d_0 and methadone-d_3 were determined by the mass fragmentographic method of Sullivan et al. [2] with some modifications; 2 ml samples were analyzed and the extraction was made with n-hexane after adding 0.05 mol/l sodium hydroxide 2 ml. The homologue 2-dimethylamino-4,4-diphenyl-5-octanone was used as the internal standard. All samples were analyzed in duplicate. The limit of sensitivity was 30 nmol/l, and the coefficient of variation was 5.5% at the 40 nmol/l level ($n = 10$).

Calculations

The areas under the plasma concentration versus time curves ($AUC_{0\text{-}t}$) were estimated by the trapezoidal rule. The residual area to infinite time ($AUC_{t\text{-}\infty}$) was obtained by $AUC_{t\text{-}\infty} = C/\beta$, where C is the observed plasma concentration at the last sampling time t and β is the average of the disposition rate constants for oral and intravenous administration calculated from the terminal parts of the semi-logarithmic plasma concentration versus time curves using linear regression analysis. The bioavailability ($F_{\%}$) was determined from

$$F_{\%} = \frac{(AUC_{0\text{-}\infty})_{oral} \cdot 100}{(AUC_{0\text{-}\infty})_{i.v.}} \cdot \quad (1)$$

The data from plasma concentration measurements after the intravenous doses were fitted to the biexponential function

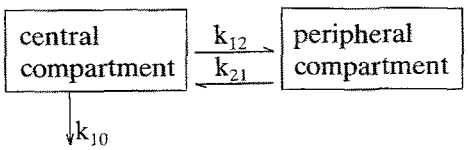
$$C = Ae^{-\alpha t} + Be^{-\beta t} \quad (2)$$

with the aid of the NONLIN program [3] on an IBM 370 digital computer. C is plasma concentration, t is time, A and B are constants, and α and β are hybrid rate constants. The data points were weighted according to

$$W_i = \frac{N \cdot 1/y_i^2}{\sum_{i=1}^{N} 1/y_i^2}, \quad (3)$$

where W_i is the eight, y_i the value of the ith observation, and N the number of data points.

From the values obtained for A, B, α and β, the values of k_{10}, k_{12} and k_{21} in the following model were calculated [4].



The apparent volume of the central compartment (V_c) was obtained from $V_c = X_0/(A + B)$, where X_0 is the intravenous dose. The volume of distribution during the post-distributive phase (V_B) was calculated from $V_B = V_c \cdot k_{10}/\beta$ and the body clearance (Q_B) from $Q_B = V_c \cdot k_{10}$.

[1] Supplied by ACO Läkemedel AB, Sweden. The tablets disintegrated within 2.2 min and showed complete dissolution within 15 min (determined according to The United States Pharmacopeia, Volume 18)

Table 2. Time to peak plasma level, area under the plasma level-time curve and bioavailability after simultaneous adiministration of methadone tablets and intravenous injection of deuterium-labelled methadone

Subject	Range of urinary pH (0–48 h after dose)	Time to peak plasma level after oral dose [h]	AUC_{oral} [μmol · l^{-1} · h]	$AUC_{i.v.}$ [μmol · l^{-1} · h]	Bioavailability [%]
1	6.4–8.4	5	6.94	16.9	41
2	6.4–7.8	4	9.31	9.41	99
3	5.0–5.7	2	2.27	3.00	76
4	5.1–6.2	2	16.0	17.2	93
5	6.6–7.7	4	5.51	6.11	90
6	6.0–8.4	1	10.4	11.5	90
7	5.3–7.2	4	3.23	6.06	53
8	5.0–5.5	2	6.14	6.73	91
Mean		3	7.48	9.61	79
SD		1.4	4.40	5.23	21

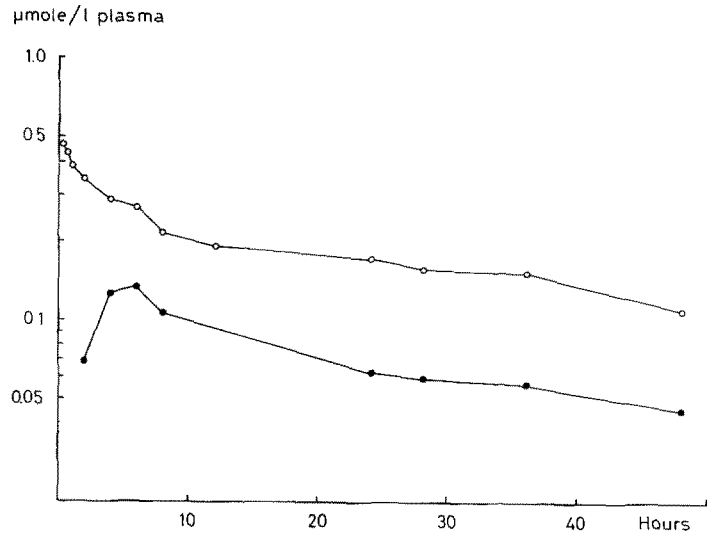


Fig. 1. Plasma levels of methadone-d_0 (●——●) and methadone-d_3 (○——○) in Subject 1 after simultaneous oral and intravenous administration of methadone hydrochloride 20 mg as tablets and deuterium-labelled methadone hydrochloride 20 mg, respectively

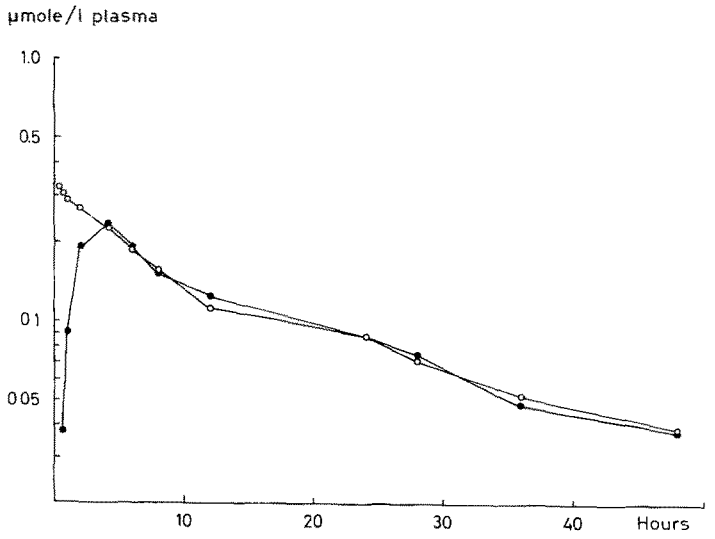


Fig. 2. Plasma levels of methadone-d_0 (●——●) and methadone-d_3 (○——○) in Subject 5 after simultaneous oral and intravenous administration of methadone hydrochloride 20 mg as tablets and deuterium-labelled methadone hydrochloride 20 mg, respectively

Table 3. Pharmacokinetic parameters of deuterium-labelled methadone following intravenous administration of a single dose. Results are from computer fit to a two compartment open model. Figures in brackets are standard deviations

Subject	A [μmol · l^{-1}]	B [μmol · l^{-1}]	α [h^{-1}]	$t_{½\alpha}$ [h]	β [h^{-1}]	$t_{½\beta}$ [h]	k_{12} [h^{-1}]	k_{21} [h^{-1}]	k_{10} [h^{-1}]	V_c [l · kg^{-1}]	V_B [l · kg^{-1}]	Q_B [ml · min^{-1} · kg^{-1}]	r[a]
1	0.245 (0.026)	0.238 (0.011)	0.357 (0.029)	1.94	0.0149 (0.0018)	46.5	0.159	0.184	0.0290	1.98	3.85	0.957	0.995
2	0.242 (0.026)	0.207 (0.014)	0.164 (0.020)	4.22	0.0255 (0.0019)	27.2	0.0534	0.0894	0.0468	1.83	3.35	1.43	0.994
3	0.234 (0.097)	0.173 (0.060)	0.348 (0.050)	1.99	0.0820 (0.0334)	8.46	0.0888	0.195	0.146	2.52	4.53	6.13	0.974
4[b]	–	0.387	–	–	0.0258	26.9	–	–	–	–	2.05	0.882	–
5	0.182 (0.021)	0.156 (0.011)	0.214 (0.013)	3.24	0.0291 (0.0026)	23.8	0.0742	0.114	0.0543	2.24	4.18	2.02	0.998
6	0.205 (0.018)	0.196 (0.011)	0.324 (0.039)	2.14	0.0196 (0.0013)	35.4	0.137	0.169	0.0376	1.81	3.48	1.13	0.996
7	0.157 (0.018)	0.114 (0.008)	0.180 (0.012)	3.85	0.0217 (0.0025)	31.9	0.0691	0.0880	0.0443	2.75	5.61	2.03	0.992
8	0.282 (0.041)	0.153 (0.015)	0.211 (0.023)	3.29	0.0284 (0.0030)	24.4	0.0820	0.0927	0.0646	1.89	4.29	2.03	0.994
Mean	0.221 (0.042)	0.203 (0.083)	0.257 (0.083)	2.95 (0.93)	0.0309 (0.0212)	28.1 (10.9)	0.0948 (0.0385)	0.133 (0.048)	0.0604 (0.0394)	2.15 (0.37)	3.92 (1.03)	2.08 (1.71)	

[a] r = the correlation coefficient between observed and predicted values

[b] A and α could not be calculated because there were insufficient data to characterize the kinetics of the distribution phase. B and β were obtained from the terminal part of the semi-logarithmic curve using linear regression analysis. V_B was calculated from $X_o/(\beta \cdot AUC)$ and Q_B from X_o/AUC

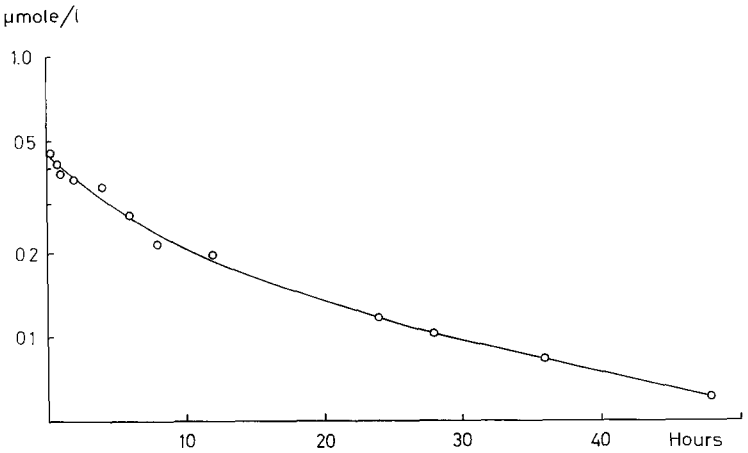


Fig. 3. Experimental (o) and computer-calculated (solid line) plasma levels of methadone-d_3 in Subject 2 following an intravenous dose of deuterium-labelled methadone hydrochloride 20 mg

Results

The results of the bioavailability determinations are given in Table 2. The peak plasma level after administration of the tablets occurred at 3 h (range 1 to 5 h). Five patients had a bioavailability exceeding 90%. Three patients had bioavailabilities between 41 and 76%. The plasma concentration versus time curves of two patients, one with a low and the other with a high bioavailability, are shown in Figs. 1 and 2.

The computer-calculated pharmacokinetic parameters for methadone after intravenous administration of a single dose are shown in Table 3. The microscopic rate constants, distribution volumes and body clearances are also given.

The experimentally determined and the theoretically calculated values in each patient agreed well, as is further shown in Fig. 3. Between patients, however, there was considerable variation. Thus, the $t_{½\alpha}$ values varied between 1.9 and 4.2 h and the $t_{½\beta}$ val-

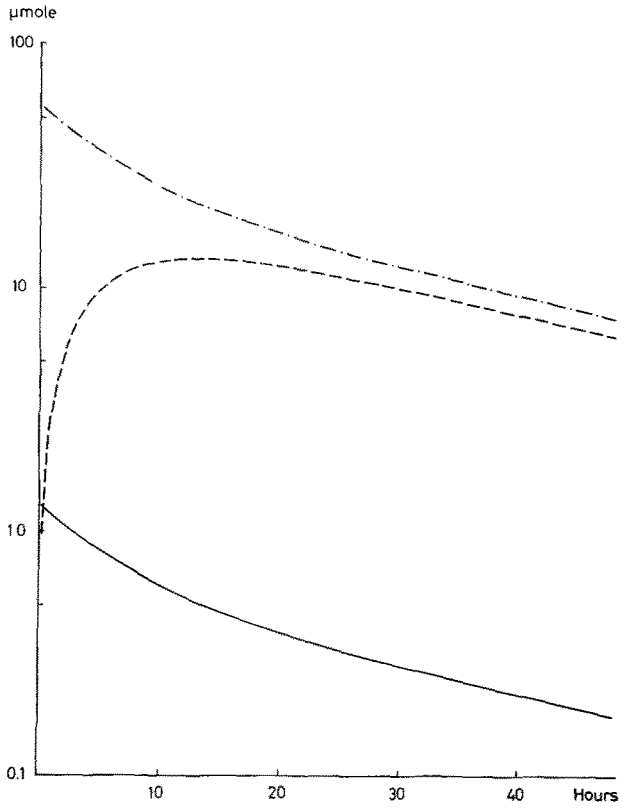


Fig. 4. Computer-calculated amounts of methadone-d_3 versus time in Subject 2 in the central (– · –) and peripheral (– –) compartment and in plasma (——) following an intravenous dose of deuterium-labelled methadone hydrochloride 20 mg. The amount in plasma was obtained by assuming a plasma volume of 42 ml per kg body weight [5]

ues between 8.5 and 47 h. Agreement was good between the elimination half-lives of unlabelled and labelled drug in the same patient. The body clearances varied between 0.96 and 6.1 ml/min/kg. The apparent volumes of distribution (V_B) were relatively high and varied between 2.1 and 5.6 l/kg.

The computer-calculated amounts of methadone in the central and peripheral compartments and in plasma for Patient 2 are shown in Fig. 4.

Discussion

The times for peak plasma levels after administration of the tablets are in accordance with values obtained previously, both by us and others [6, 7, 8], after oral administration of methadone solution. Thus, the absorption rate of methadone from these tablets and from a solution seems to be comparable.

The simultaneous administration of oral and intravenous doses in bioavailability studies eliminates errors due to any variation in distribution and elimination kinetics at different times. The technique using a stable isotope-labelled analogue of the drug has been employed before, e. g. in determination of the bioavailability of N-acetylprocainamide [9]. It is important to note that the elimination kinetics does not seem to differ between labelled and unlabelled methadone, as the half-lives were in close agreement. There is, therefore, no evidence of kinetic isotope effects altering the disposition of the deuterated methadone.

According to our results the bioavailability of methadone is higher than previously assumed. Beaver et al. [1], in a study in cancer patients, reported the biological availability of oral methadone to be 45%. It should be realized that Beaver's study based the assessment of bioavailability on patient's self-rated experience of pain in a cross-over design. This method may be expected to have lower precision than the chemical measurements used in the present study. Another possible explanation for the higher bioavailability found here could be the difference in patient populations.

The reason for the low biological availability reported by Beaver et al. [1] in cancer patients, and by us in two of eight patients, is not known. It may possibly be related to self-induction of metabolism, which has been shown to occur in experimental animals and in some patients on methadone maintenance therapy [10, 11]. It is possible that previous treatment with narcotics in the cancer patients and self-administration of heroin and other drugs in the present series of addicts could have influenced the first-pass elimination of methadone. The mechanism behind the limited biological availability in certain individuals needs to be separately studied.

Beta-phase plasma half-lives of the same order of magnitude as in this study have previously been reported [6, 8]. Our half-live values varied considerably between patients. Some of the variation can probably be attributed to the differences in urinary pH. In another paper it will be shown that the half-life in some subjects is about twice as long with an alkaline urine as with an acid urine [12].

The high volumes of distribution indicate that the amount of methadone in plasma is very small (around 1%) compared with the total amount in the body (see Fig. 4). The values of the microscopic constants k_{12}, k_{21} and k_{10} show that the peripheral compartment equilibrates fairly rapidly with plasma. A three compartment model was also tried, but did not give a better fit to the experimental data. The failure to detect a deep compartment may depend on its small size compared to the others, or on the relatively short observation period (48 h).

The major findings in the present study relate to the application of new methodology to study the oral bioavailability of methadone. In the treatment of pain in the terminally ill, and in the management of opiate-dependent subjects, it sometimes becomes necessary to change from oral to parenteral medication or the converse. In view of the narrow therapeutic range of narcotic analgesics, it appears safer in future to assume that oral methadone has a systemic availability ranging from 50 to 100%. In going from oral to parenteral therapy the safest course would be to reduce the dose by *half* and to be prepared to increase it according to the patient's needs. In changing from parenteral to oral therapy, on the other hand, the *full* dose may be given initially, with a further increase if necessary.

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Dr. U. Meresaar
Hospital Pharmacy
Ulleråker Hospital
S-750 17 Uppsala
Sweden