Kinetic disposition of morphine in young males after intravenous loading and maintenance infusions

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Loading and maintenance infusions of morphine sulfate were administered to 5 young male patients 23–34-yr-old prior to elective surgery. Apparent steady-state plasma concentrations were achieved 30 minutes after the start of the drug infusion. The volume of distribution at steady-state (2.43 ± 0.48 L·kg^{-1}), beta elimination rate constant (0.700 ± 0.162/h) and plasma clearance (1.66 ± 0.33 L·kg^{-1}·h^{-1}) were similar to values previously determined in young healthy subjects receiving a single bolus infusion. These data confirm our findings concerning morphine disposition in healthy young subjects and demonstrate the feasibility of achieving predictable plasma concentrations of morphine for future assessment of pharmacodynamic/pharmacokinetic relationships for this drug.

Key words

We previously reported results of a study on age and the kinetic disposition of morphine after intravenous bolus infusions.[1] The disposition constants we derived were somewhat different from those reported by others.[2–5] Our data indicated a smaller apparent volume of distribution and an increased plasma clearance of morphine. We attribute this difference to the fact that previous studies utilized a radioimmunoassay which is susceptible to interference by morphine-3-glucuronide.[6] Our study utilized a specific extraction and chromatographic method.[7] Since kinetic data are only useful if they can be used to predict drug concentrations in patients, we administered loading and maintenance infusions of morphine sulfate to young male patients prior to elective surgery. Doses based on our previous kinetic disposition data were used to produce predictable steady-state plasma concentrations of the drug. The results of this investigation are presented below.

Methods

Patient selection

Five male subjects, 23–34 years old, who weighed 67–97 kg, were enrolled in the study. They were unmedicated patients who were scheduled for elective surgery. This study was approved by the University of Manitoba Faculty Committee on the Use of Human Subjects in Research, and informed consent was obtained from all volunteers. Routine laboratory investigations, including haemoglobin concentration, total white blood cell and platelet counts, and serum glucose, urea nitrogen, creatinine, protein, albumin, glutamic oxaloacetic trans-

aminase, glutamic pyruvic transaminase, lactic dehydrogenase and alkaline phosphatase were done to confirm normal values for age, especially for hepatic and renal function.

Study design
All studies were conducted in an operating theatre in the morning and prior to surgery. Morphine sulfate was administered by two infusion pumps, one of which was used for the loading dose and the other for a simultaneous maintenance infusion through an indwelling catheter in a forearm vein. Subjects were recumbent throughout the study. The drug dose was calculated to achieve predicted steady-state concentrations in plasma based upon our previous bolus infusion experiments in young healthy volunteers.[1] The dose regimens were chosen to produce two different steady-state plasma concentrations of morphine in each patient. By repeating the loading dose and doubling the maintenance infusion rate, the morphine plasma concentration was expected to double after the second loading dose.

Target concentrations of 32 and 64 $ng\cdot ml^{-1}$ were initially chosen, and using the relationship plasma concentration at steady-state (C_{ss}) = infusion rate (K_0)/clearance (Cl_p), maintenance infusion rates of 0.068 and 0.137 $mg\cdot kg^{-1}\cdot h^{-1}$ were calculated along with corresponding loading doses of 0.19 $mg\cdot kg^{-1}$.[8] The first patient who received this regimen became very sleepy with the second loading dose, and for the remaining four subjects the loading and maintenance doses were halved to avoid sedation. The target morphine concentrations for these patients were 16 and 32 $ng\cdot ml^{-1}$, and the calculated loading and maintenance doses were 0.10 $mg\cdot kg^{-1}$ and 0.034 and 0.068 $mg\cdot kg^{-1}\cdot h^{-1}$ respectively.

Loading doses were given over 15 minutes and each maintenance dose was continued over 60 minutes. At the end of the second hour, the administration of morphine sulfate was discontinued.

Sample preparation and analyses
Venous blood samples (5 ml) were withdrawn from the opposite arm through an indwelling catheter into glass syringes at the following times: 0 (start of infusions), 5, 15, 30, 45, 60, 75, 90, 105, 120 (end of infusions), 135, 150, 180, 240 and 300 minutes.
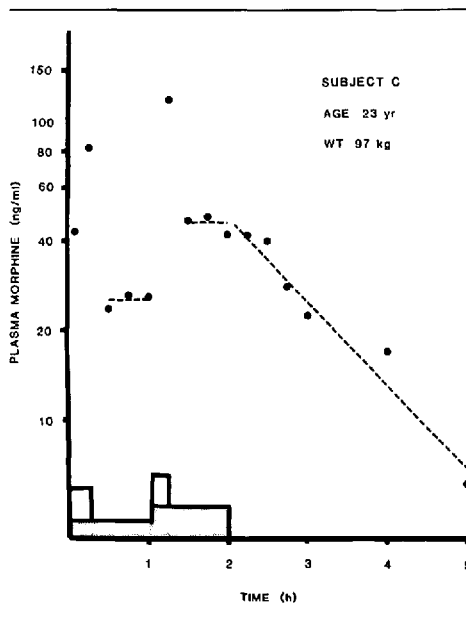

FIGURE   Plasma morphine concentration-time curve for the subject who most closely represents the mean data from the low dose regimen. Morphine concentrations are presented as nanograms free base per milliliter of plasma. The shaded bars indicate the continuous maintenance infusion which was doubled between one and two hours after the start of the first loading dose. The open bars represent the two loading infusions which were given one hour apart.

Blood was immediately transferred to tubes containing sodium oxalate and mixed. Plasma was separated by centrifugation and stored (-20° C) for subsequent morphine analysis by high performance liquid chromatography.[7] All morphine concentrations are reported as the free base (86 per cent of weight as morphine sulfate).

Data analyses
The terminal elimination rate (beta) was determined by least squares linear regression analysis of the log of the plasma concentration of morphine versus time from the end of infusion at two hours to five hours after the start of the experiment. Volume of distribution (Vd_{area}) and plasma clearance (Cl_p) were determined at one and two hours after the start of drug infusions assuming that steady-state was achieved. Plasma clearance was calculated as the maintenance infusion rate divided by the mean morphine plasma concentration from 30–60 and

TABLE I   Pharmacokinetic disposition of morphine in young male patients after loading and maintenance doses

Subject	Age (yr)	Weight (kg)	Beta (h⁻¹)	Vd_{area}‡ $(L{\cdot}kg^{-1})$			Cl_p $(L{\cdot}kg^{-1}{\cdot}h^{-1})$		
				t = 30–60 min	t = 90–120 min	Model independent estimate	30–60* min	90–120* min	Model† independent estimate
A	25	68	0.927	2.62	1.50	1.90	2.43	1.39	1.76
B	24	67	0.728	2.34	2.75	3.02	1.70	2.00	2.20
C	23	97	0.640	2.05	2.53	2.34	1.31	1.62	1.50
D	26	88	0.725	1.56	2.40	2.07	1.13	1.74	1.50
E	34	80	0.480	3.54	3.92	2.83	1.70	1.88	1.36
Mean	26	80	0.700	2.42	2.62	2.43	1.65	1.73	1.66
± SD	4	13	0.162	0.74	0.87	0.48	0.50	0.24	0.33

*$Cl_p = K_O/C_{ss}$.
†Cl_p = Dose/$AUC_{0{\to}\infty}$.
‡Vd_{area} = Cl_p/beta.

90–120 minutes. Vd_{area} was calculated as Cl_p/beta for these same times. Using model independent equations, Cl_p (dose/area under the plasma concentration vs time curve (AUC) from t = 0 → ∞) and Vd_{area} (Cl_p/beta) were also calculated for the data overall. Area under the curve was determined by the trapezoidal method and residual area under the curve after the last data point was determined as plasma concentration/beta.[9] Data in the text are presented as means ± SD. Means were compared by analysis of variance.

Results

A morphine concentration-time curve for the patient who most closely approximated the mean values of kinetic disposition in our study is presented in the Figure. These data were derived from the low dose regimen, i.e., loading doses of 0.1 mg·kg⁻¹ with maintenance doses of 0.034 and 0.068 mg·kg⁻¹·h⁻¹ of morphine sulfate. The morphine concentration in plasma stabilized within 30 minutes of the loading doses and declined exponentially after two hours when the drug infusion was stopped.

A summary of the kinetic disposition of morphine in the five subjects is presented in Table I. Vd_{area} and Cl_p determined between 30–60 and 90–120 minutes during the infusion were similar and agreed with the overall estimate of these disposition constants calculated by model independent methods. Thus they were not different relative to the method or time of determination. The measured morphine plasma concentrations at apparent steady-state approximated the target concen-

TABLE II   Comparison of observed plasma morphine concentrations at steady-state with predicted values based on model independent kinetic analysis of the plasma concentration versus time data from each volunteer (see Table I). Subjects A–D received the low dose regimen. Subject E received a higher dose regimen

Subject	Time interval (min)	C_{ss} $(ng{\cdot}ml^{-1})$		
		Predicted	Derived	Observed
A	30–60	16	16	14
	90–120	32	33	49
B	30–60	16	13	20
	90–120	32	26	34
C	30–60	16	19	26
	90–120	32	39	42
D	30–60	16	19	30
	90–120	32	39	39
Mean	30–60	16	17 ± 3	23 ± 7
±SD	90–120	32	34 ± 6	41 ± 6
E	30–60	32	43	40
	90–120	64	86	73

trations as predicted by our previous study, and of course closely agreed with those derived from the kinetic parameters found for each individual (Table II). As well, Table III indicates that the kinetic parameters observed in this study also agree with those determined in our previous study.[1]

Discussion

Our data indicate that steady-state concentrations for morphine were achieved within 30 minutes of

TABLE III Comparison of the pharmacokinetic disposition of morphine after intravenous bolus and maintenance infusions compared to a single bolus infusion in young subjects. Data are presented as ranges or as means ± SD

	Bolus infusion* (13)†	Loading and maintenance infusions§(5)†
Age (yr)	23–28	23–34
Weight (kg)	55–93	67–97
Vd_{area} ($L \cdot kg^{-1}$)	2.73 ± 0.55‡	2.43 ± 0.48
Cl_p ($L \cdot kg^{-1} \cdot h^{-1}$)	2.02 ± 0.30	1.66 ± 0.33
Beta (/h)	0.77 ± 0.20	0.70 ± 0.16

*Data from reference 1.
†Number of experimental subjects.
‡Data recalculated from reference.[1]
§Vd_{area} and Cl_p data from model independent determinations. See Table I.

the start of the loading dose (Figure), and that these concentrations agreed reasonably well with target concentrations based on our previous data. As Tables II and III indicate, there are no statistically significant differences in any of the kinetic constants for the two methods of morphine administration in young, healthy subjects. If steady-state had not been achieved, estimations of Cl_p and Vd_{area} would have been different, depending on the time and method used for their determination. Thus the present studies confirm our previously reported kinetic data using a specific chemical assay for morphine and demonstrate that these data are appropriate for the determination of dosage regimens which can produce predictable plasma morphine concentrations in man.

It is of interest that this study confirms our previous finding that plasma clearance of morphine exceeds hepatic blood flow ($1.26 L \cdot kg^{-1} \cdot h^{-1}$).[10] Other data suggest that the kidney is important for the conjugation of morphine with glucuronic acid, and this extrahepatic metabolic site probably accounts for the discrepancy between hepatic blood flow and plasma clearance of morphine.[11,12]

Our observed plasma concentrations of morphine at apparent steady-state were slightly higher than predicted from our previous data.[1] This difference may be explained by the fact that plasma clearance of morphine in these five volunteers was somewhat lower than in our previous study. This could be due to the fact that subjects were resting and recumbent in the present study and ambulatory in our previous

investigation. Cardiac output would be expected to be lower at rest.

In conclusion, the present study confirms the feasibility of using morphine infusion regimens to assess relationships between plasma concentrations and effects in young adults. Our results are also supported by a recent report of a similar approach to the production of steady-state morphine plasma concentrations in young chidren.[13]

Acknowledgements

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Résumé

Avant la chirurgie élective des perfusions de sulfate de morphine ont été administrés à cinq jeunes patients âgés de 23 à 34 ans. Les concentrations plasmatiques stables ont été acquises 30 minutes après le début de la perfusion. Le volume de distribution (2.43 ± 0.48 L·kg⁻¹), la constante bêta du taux d'élimination (0.700 ± 0.162/h) et la clearance plasmatique (1.66 ± 0.33 L·kg⁻¹·h⁻¹) étaient similaires à des valeurs déterminées au préalable chez les jeunes sujets en bonne santé recevant un bolus unique. Ces données confirment nos résultats concernant la disposition de la morphine chez les jeunes sujets sains et démontrent la possibilité d'acquérir des concentrations plasmatiques prévisibles de morphine afin d'évaluer dans le futur la relation phamacokinétique/phamacodynamique de cet agent.