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Pharmacokinetics of Intravenous Morphine in Patients Anesthetized with Enflurane–Nitrous Oxide

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Morphine is used as an anesthetic supplement. Its disposition in surgical patients under enflurane–nitrous oxide anesthesia has not been determined. Available data on morphine concentrations in plasma after equivalent intravenous doses are conflicting, possibly as a result of varying degrees of specificity of the analytical methods for the unchanged, pharmacologically active form of the drug. This study determined the pharmacokinetics of morphine (0.05, 0.1, 0.14, or 0.2 mg/kg) injected intravenously in 10 surgical patients anesthetized with enflurane–N_2O–O_2. Arterial plasma was analyzed for unchanged morphine and conjugated morphine. Specificity of the analytical procedure for unchanged morphine was achieved by the combination of solvent extraction and radioimmunoassay techniques. Kinetic indices were derived by nonlinear least-squares analysis of log concentration (ng/ml) *vs.* time relationships. Morphine disposition was independent of dose in this fourfold range and was best described by a three-compartment model with a mean elimination half-time ($t_{1/2\beta}$) of 104 ± 5 min. The apparent volumes of distribution (V_d) and of the central compartment (V_1) were 3.4 ± 0.2 and 0.13 ± 0.02 l/kg, respectively, while the clearance (Cl_B) was 23 ± 1 ml·min^{-1}·kg^{-1}. Extraction of morphine by the liver appeared to be complete. Conjugated morphine was eliminated from plasma with a $t_{1/2\beta}$ of 169 ± 15 min. The ultimate elimination of morphine from the body was dependent upon its reuptake from slowly perfused peripheral tissues, $k_{10} > k_{31}$ ($P < .001$). (Key words: Analgesics, narcotic: morphine. Analgesics, intravenous: morphine. Pharmacokinetics: distribution.)

PATIENTS receive morphine intravenously under a variety of conditions during anesthesia and surgery. The pharmacokinetics of morphine in surgical patients receiving enflurane–nitrous oxide anesthesia have not been determined. There have been several reports of morphine pharmacokinetics,[1–5] but there remains some confusion about its disposition because of the differences in the investigational protocols and in methodology, especially the analytical specificity for the unchanged, pharmacologically active drug. This paper describes the pharmacokinetics of morphine administered intravenously to surgical patients receiving enflurane–nitrous oxide anesthesia. Arterial plasma was analyzed specifically for unchanged morphine by combining solvent extraction and radioimmunoassay techniques.

Methods

The investigational protocol was approved by the Human Investigations Committee at Emory University. Informed consent was obtained from 10 patients (ASA Class I or II) scheduled for elective surgery (4 vaginal hysterectomies, 4 cervical conizations, 1 anal fistulectomy, and 1 colostomy). The patients ranged in age from 18–39 years (24.8 ± 5.7 SD) and included eight females and two males. Routine preoperative tests were all normal including the hemogram, SMA-6 and SMA-12 screening, chest X-ray, and electrocardiogram. Two patients received premedication orally 2 hours before anesthesia; number 5 received 5 mg diazepam and number 11 was given 100 mg pentobarbital. Cannulae were inserted percutaneously into a forearm vein and a radial artery after infiltration of the areas with 0.5 per cent lidocaine hydrochloride. Lactated Ringer's solution containing 5 per cent dextrose was infused intravenously to a total volume of 6–8 ml/kg prior to the induction of anesthesia and subsequently maintained at a rate of 5 ml·kg^{-1}·hr^{-1}. Atropine sulfate (0.4 mg), sodium thiopental (4.3 ± 0.9 SD mg/kg), and succinylcholine (0.8 ± 0.2 mg/kg) were injected intravenously, and anesthesia was maintained with 1–2 per cent enflurane in nitrous oxide and oxygen (3:2 l/min) via an endotracheal tube for the remainder of the surgical procedure.

Once a stable level of anesthesia had been attained (approximately 1 hour after induction), a single dose of morphine sulfate (0.05, 0.1, 0.14, or 0.2 mg/kg) was injected intravenously over a 30-sec interval. There were minimal changes in blood pressure and heart rate associated with the injection; mean arterial blood pressure decreased 5 ± 8 SD per cent and recovered by 15 min. Arterial blood samples of 10–15 ml were drawn through the radial artery cannula into heparin-rinsed plastic syringes at 1, 3, 5, 7.5, 10, and 30 min after the injection of morphine and every 30 min thereafter for the duration of the study. The samples were immediately transferred to glass tubes that previously had been rinsed with heparin sodium (100 units/ml) and dried. The tubes were covered with

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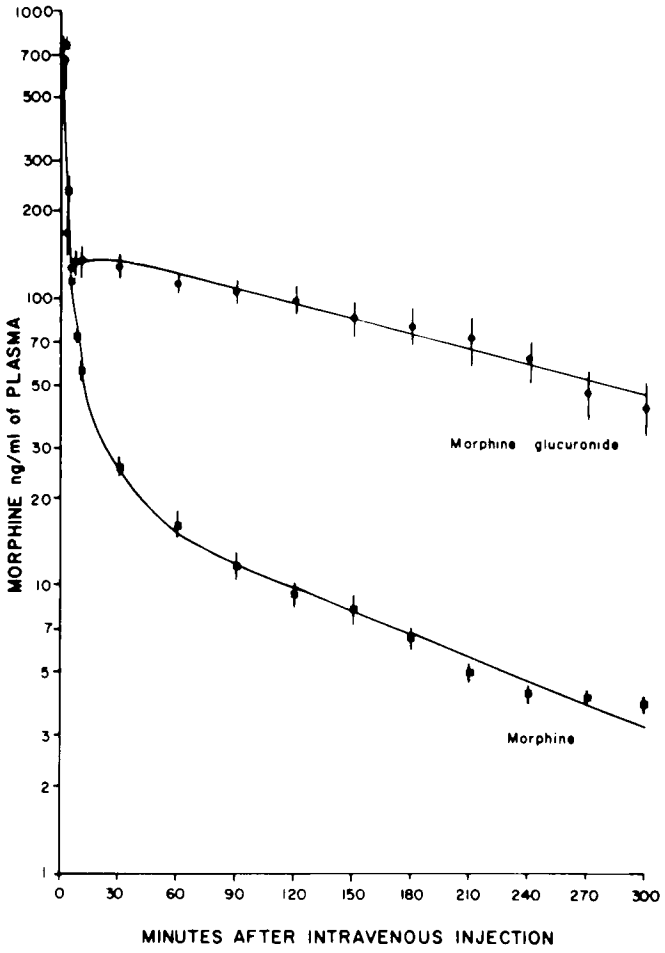

FIG. 1. Concentrations of unchanged morphine and of morphine metabolites in plasma. Each data point represents the mean ± SEM for 4 patients given morphine 0.14 mg/kg, intravenously. The curve for unchanged morphine was fitted to the mean data points by nonlinear least-squares analysis and can be described by the equation: $C_{pet} = 1290\ exp^{-0.172t} + 86.8\ exp^{-0.0752t} + 20.4\ exp^{-0.00608t}$. The half-times for the π, α, and β phases are 1.0, 9.2, and 114 min, respectively. The half-time for the elimination phase of the metabolites is 173 min.

Parafilm® and kept in ice until the plasma was separated by centrifugation. Plasma samples were stored at 4° C until the time of analysis. The duration of sampling after morphine ranged from 240–360 min (mean 282 ± 75 SD). The time from injection of morphine to the termination of enflurane anesthesia varied from 15–145 min (mean 52 ± 50 SD).

For the analysis of unchanged morphine, 1–4 ml aliquots* of plasma were brought to a total volume of 4 ml with distilled water, the *p*H was adjusted to 9–10 with 2.5 N sodium hydroxide, 3 ml of 1 M potassium phosphate (*p*H 10.4) and 5 g of sodium chloride were added, and the sample was mixed thoroughly on a Vortex® mixer. Then 10 ml of ethylene dichloride containing 10 per cent (V/V) n-amyl alcohol were added, and the mixture was shaken for 20 min. Centrifugation for 10 min at 2000 × *g* separated the solvent and aqueous phases. Eight ml of the solvent (top) phase were transferred to a clean tube containing 1 ml of 0.5 N hydrochloric acid. The mixture was shaken for 20 min and centrifuged for 10 min, and 0.5 ml of the acidic (top) phase was transferred to a glass RIA tube. The tubes were covered with Parafilm® and stored overnight at room temperature.

Morphine radioimmunoassay of the acidic extract was done by adjusting the *p*H to 7 with 1 N sodium hydroxide and incubation for 60 min at room temperature with 0.4 ml morphine ^{3}H-antiserum (Abuscreen RIA®†). Then 1 ml of saturated ammonium sulfate was added, and the mixture was allowed to stand at room temperature for 60 min before it was centrifuged at 1100 × *g* for 10 min. One-half ml of the supernatant was transferred to a glass liquid scintillation vial, 12 ml of a Bio-Solve-Dilufluor®‡ scintillation mixture were added, and the tritium radioactivity was analyzed in a Beckman LS-230® liquid scintillation spectrometer. Recoveries of known concentrations of morphine added to human plasma averaged 92 ± 9 SD per cent. Concentrations of morphine in unknown samples were determined by comparison to known standards solutions analyzed simultaneously; the loss of morphine was presumed to be the same for both known and unknown samples. The lower limit of sensitivity of the method was approximately 1 ng/ml of plasma based on a 4 ml sample aliquot.

For the analysis of "total morphine" (*i.e.*, morphine and morphine glucuronide) 0.1-ml aliquots of plasma were transferred directly to glass RIA tubes and 0.4 ml of morphine ^{3}H-antiserum (Abuscreen RIA®) were added. The mixture was incubated for 60 min at room temperature before the addition of 0.5 ml of saturated ammonium sulfate. The sample was mixed thoroughly on a Vortex® mixer, allowed to stand at room temperature for 20 min, and then centrifuged at 1100 × *g* for 20 min. One-half ml of the clear supernatant was transferred to a glass liquid scintillation vial, 12 ml of a Bio-Solve-Dilufluor® mixture were added, and the tritium radioactivity was determined in a Beckman

* Aliquots of plasma were chosen so that the final quantity of morphine in the tube ranged between 1 and 8 ng. Initially this required range-finding analysis of plasma samples before the final quantitative analysis was done in duplicate or triplicate.

† Abuscreen RIA was purchased from Roche Diagnostics, Inc. of Nutley, N. J.

‡ Bio-Solve was purchased from Beckman Instruments, Fullerton, California, and Dilufluor was obtained from Scientific Products Co., Atlanta, Georgia. The scintillation mixture was made by combining 600 ml of BBS-3 with 2400 ml of Dilufluor.

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LS-230 Spectrometer.[‡] The coefficient of variation for this RIA was 3.7 per cent.

Morphine-glucuronide concentrations were calculated as the difference between the concentrations of "total morphine" and unchanged morphine and are expressed in terms of equivalents of morphine-base. On a molar basis, the radioimmunoassay measured 89 per cent of known concentrations of morphine-3-glucuronide added to plasma compared to standard solutions of morphine in distilled water. In order to verify the specificity of the extraction method, the recoveries of known concentrations of morphine and of morphine-3-glucuronide in water and in plasma were determined; solvent extraction recovered 87 per cent of the morphine and less than 1 per cent of the morphine-glucuronide. When the sample was autoclaved in 1.2 N HCl at 121°C and 15 psi to hydrolyze conjugated morphine[6] before extraction, the molar recovery of morphine from morphine-3-glucuronide increased to 77 per cent.

The decline of unchanged morphine concentrations in plasma could be described by a triexponential time function determined by the nonlinear least squares method of residuals as described by Gibaldi and Perrier and modified for use as a computer program.[7,8] In all cases the coefficient of determination (r^2) was greater than 0.994. Pharmacokinetic variables were calculated using standard equations (see the Appendix).

Data are expressed as the mean ± standard error of the mean unless designated otherwise. Student's *t* test was used for group comparisons with $P < .05$ as the minimal limit of statistical significance. The *F* ratio test was used to determine the suitability of fitting a triexponential *vs.* a biexponential equation to the plasma concentration vs time data for each patient.[9]

Results

Morphine elimination from plasma could be described by a triexponential equation (fig. 1) and its pharmacokinetics represented by a three-compartment model (fig. 2).§ The concentration of morphine in plasma decreased rapidly following intravenous injection, and by 10 min, 96 to 98 per cent of the injected dose had been cleared from plasma in all patients. Thereafter, the decline of morphine concentrations was more gradual and the terminal elimination phase had an average half-time ($t_{1/2\beta}$) of 104 ± 5 min for all 10 patients (table 1). The calculated volumes of distribution and clearance were

§ A triexponential equation provided a significantly (*F*-ratio test[9]) better description of the data than did a biexponential equation for all of the patients except number 6 for which either equation was equally satisfactory.

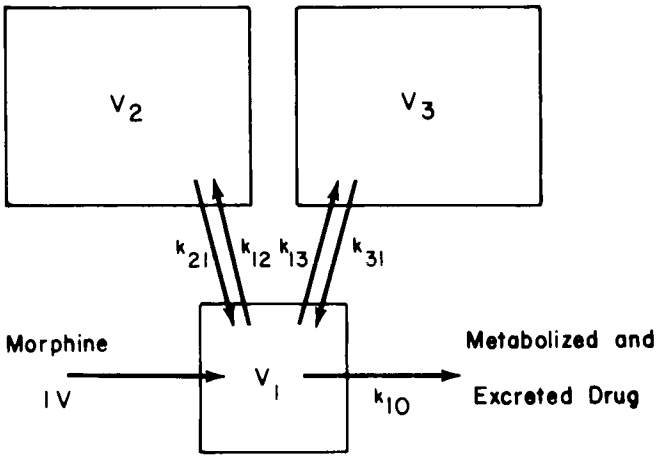

FIG. 2. Three-compartment model of the disposition of morphine in man. See Appendix and table 1.

independent of dose. The rate constant, k_{31} representing return of morphine from one of the peripheral compartments, was considerably lower in each case than the elimination constant K_{10} ($P < .001$), indicating that return of the drug from this peripheral compartment was the rate limiting step in the ultimate elimination of morphine from the body.

Figure 1 also shows the relationship between the concentration of unchanged morphine and that of conjugated morphine in plasma of patients receiving 0.14 mg/kg (10 mg/70 kg). Similar data were obtained for all doses. In each case, the concentrations of conjugated morphine exceeded those of the unchanged drug within 10 min after the injection, and by 90 min the metabolites represented more than 90 per cent of the total morphine in plasma. The elimination of conjugated morphine from plasma ($t_{1/2\beta}$ = 169 ± 15 min) was slower than that of the unchanged drug.

Discussion

Morphine is frequently used intravenously to supplement inhalational anesthetics in surgical patients. This study determined the pharmacokinetics of morphine administered intravenously in a fourfold range of doses (0.05–0.2 mg/kg) under clinical conditions in patients receiving enflurane–nitrous oxide anesthesia. The analytical method combining solvent extraction and radioimmunoassay measured only unchanged morphine and excluded its metabolites, principally morphine glucuronide.

Three distinct phases of morphine elimination from plasma were evident in each patient. The first (π) phase has been reported,[4,5] but not consistently, probably because of the lack of frequent blood sampling at the early times following intravenous injection.[1–3] Both the first (π) and second (α) phases

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TABLE 1. Kinetic Parameters Calculated for the Disposition of Intravenously Administered Morphine in Surgical Patients*

Patient Number	Dose (mg/kg)	Body Weight (kg)	$t_{1/2}$ (min)			V_1 (l/kg)	V_d (l/kg)	Cl_B (ml·kg^{-1}·min^{-1})	Transfer Rate Constants (min^{-1})				
			π	α	β				k_{10}	k_{12}	k_{21}	k_{13}	k_{31}
7	0.05	43.6	0.5	4	101	0.07	3.4	23	.342	.488	.344	.365	.015
5	0.1	45.0	1.5	9	88	0.19	2.9	23	.123	.153	.135	.128	.017
6	0.1	55.0	1.6	9	104	0.23	4.5	30	.133	.126	.117	.130	.014
	Mean		1.5	9	96	0.21	3.7	25	.128	.140	.126	.129	.016
11	0.14	86.4	1.1	10	111	0.10	3.2	20	.202	.189	.106	.186	.013
12	0.14	60.5	0.9	12	147	0.08	4.9	23	.298	.241	.089	.203	.008
13	0.14	58.2	1.0	8	105	0.14	3.9	26	.181	.254	.145	.218	.015
14	0.14	40.9	1.1	15	105	0.12	3.3	22	.182	.254	.079	.151	.013
	Mean (±SEM)		1.0 (0.05)	11 (1)	117 (10)	0.11 (0.01)	3.8 (0.4)	23 (1)	.216 (.028)	.234 (.015)	.105 (.014)	.190 (.014)	.012 (.002)
8	0.2	58.6	1.1	5	107	0.13	2.7	18	.132	.179	.226	.234	.019
9	0.2	43.2	1.1	6	90	0.15	2.6	20	.136	.179	.197	.205	.021
10	0.2	59.5	1.2	9	87	0.15	3.2	26	.175	.181	.121	.149	.016
	Mean (±SEM)		1.1 (0.04)	7 (1)	94 (6)	0.14 (0.005)	2.8 (0.2)	21 (2)	.148 (.014)	.180 (.001)	.181 (.031)	.196 (.025)	.019 (.001)
All (n = 10)	Mean ± (SEM)	55.1 4.3	1.2 (0.07)	9 (1)	104 (5)	0.13 (0.02)	3.4 (0.2)	23 (1)	.190 (.023)	.224 (.032)	.156 (.025)	.197 (.022)	.015 (.001)

* See Appendix for abbreviations and equations for calculating pharmacokinetic variables.

represented primarily distribution of morphine to tissues and organs. The average values for these distribution phases were close to those reported by Stanski *et al.*[4] for larger doses in adults and by Dahlström *et al.*[5] for analgesic doses in children of 1–5 years. The half-time of the elimination (β) phase was consistent for the four doses and averaged 1.7 hours. Previous clinical investigations using analytical methods specific for unchanged morphine have reported terminal elimination half-times approximating 2 hours.[1,5] It is not possible to determine from the available data just what, if any, effect enflurane–nitrous oxide anesthesia had on the disposition of morphine. Anesthesia appears to have had little effect on the half-time for the ultimate elimination of morphine from plasma.

Hepatic extraction and biotransformation of morphine are thought to be relatively complete.[10] If it is assumed that morphine is eliminated only by its biotransformation in the liver and that liver blood flow is about 21 ml·min^{-1}·kg^{-1},[11] then extraction of morphine by the liver was complete in the present study ($Cl_B = 23 \pm 1$ ml·min^{-1}·kg^{-1}). Thus, hepatic blood flow represents a rate limiting step for morphine elimination from the body. Disease states and anesthetics that decrease hepatic blood flow will decrease elimination. Another mechanism that may govern the elimination of morphine is its reuptake from slowly perfused tissues (represented by V_3 in fig. 2) since the values of k_{10} were 6–37 times those of k_{31}. The relative importance of each of these mechanisms remains to be determined.

The major mechanism of morphine elimination from the body is conjugation with glucuronic acid, primarily in the liver.[10] Conjugated morphine was present in the earliest sample of plasma taken 1 min after injection and its concentration exceeded that of the unchanged drug by almost 10-fold within 90 min. Its elimination from plasma was slower than that of the unchanged drug. These observations may explain some of the discrepancies between the findings of investigators who have used solvent extraction techniques specific for unchanged morphine.[1,5] and others who have employed a radioimmunoassay (RIA) for morphine.[2–4,12] Concentrations of morphine in plasma of patients given an equivalent intravenous dose (10 mg/70 kg) were approximately three times greater when estimated by RIA than those estimated by solvent extraction techniques (table 2) except for the one study by Stanski *et al.*[4] The ratio between unchanged and conjugated morphine in plasma 4 hours after an intravenous injection of 0.14 mg/kg was approximately 1:15 in the present study and 1:11 in the report by Brunk and Delle.[1] In the estimates based on RIA, the ratio of unchanged to conjugated drug was only 1:4.[2] The latter would be expected if the assay was measuring some of the metabolite as unchanged drug. As Catlin has demonstrated, there may be considerable variation in the degree of cross-reactivity of different batches of RIA anti-

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TABLE 2. Morphine Concentrations in Plasma at Several Times After an Intravenous Dose of Morphine Sulfate or Hydrochloride (10 mg/70 kg or 0.14 mg/kg)

Investigators	Analytical Method	Experimental Conditions	Concentration of Morphine Base (ng/ml)			
			30 min	60 min	120 min	240 min
Murphy & Hug	Solvent extraction & RIA*	Adult patients, enflurane–N_2O anesthesia	24	17	9	7
Dahlström *et al.*[5]	Solvent extraction & GLC†	Pediatric patients, N_2O–pancuronium anesthesia	37	16	11	6
Brunk & Delle[1]	Solvent extraction & ^{14}C-counting	Adult volunteers, awake	32	20	15	—
Stanski *et al.*[4]	RIA	Adult volunteers, awake	27	23	18	11
Berkowitz *et al.*[2]	RIA	Adult patients, general or regional anesthesia	82	53	29	—
Yang *et al.*[12]	RIA	Adult volunteers, awake	80	51	37	20

* RIA = Radioimmunoassay.

† GLC = Gas/liquid chromatography.

bodies with morphine and its metabolites,[13]¶ and this probably explains differences in the levels of morphine estimated by different investigators using different batches of RIA antibodies.[2–4,12]

Differences in analytical specificity obviously affect the pharmacokinetic values calculated from drug concentration data. Comparing those studies that appear to have measured only unchanged morphine in plasma, we find that the terminal elimination half-times range from 1.7–2.3 hours, which is not much different from estimates based on the RIA method (2.0–2.7 hours) although the agreement is probably coincidental. Estimates of distribution volumes and plasma clearance appear to be more variable among all studies (V_d = 1.0–3.4 l/kg; Cl = 6–23 $ml \cdot min^{-1} \cdot kg^{-1}$). These differences may reflect the specificity of analytical techniques as well as many other variables (*e.g.*, age, physical status, anesthetic and surgical conditions) that will have to be sorted out under carefully controlled experimental conditions.

Despite the three- to fourfold difference in pharmacokinetic variables, all of the studies point to a widespread distribution of morphine in the body (large V_d) and a fairly rapid elimination of the drug from plasma (short $t_{1/2\beta}$ and rapid Cl). It appears that it is eliminated more rapidly from plasma than from the central nervous system,[16] and this may explain the relatively long duration of action of morphine despite its brief half-time of elimination from plasma.[12,17]

It is interesting to note that the half-time for elimination of morphine is considerably shorter than that for fentanyl (3.5–5.5 hours), which is considered to be a short-acting narcotic analgesic.[18] Fentanyl is short-acting after a single small dose because its concentrations in blood and brain fall to low levels owing to its rapid uptake into other tissues; the ultimate elimination of fentanyl from the body is slow, and there is accumulation of fentanyl and prolongation of its effects after repeated or very large doses.[8,19] Large doses of fentanyl have a longer duration of action because its uptake by other tissues does not decrease its blood and brain concentrations below threshold levels.[8] In the case of morphine, effective levels persist in the central nervous system even though the concentration of morphine in plasma falls.[16,17] Therefore, the intensity and duration of action of morphine cannot be predicted solely on the basis of its concentration in plasma.[12] It is likely that there will be less accumulation of morphine than of fentanyl when intravenous doses are repeated to maintain or to restore its effects.

In conclusion, morphine elimination from plasma can be described by a three-compartment open model, and its kinetics appear to be independent of dose in the fourfold range reported here. Biotransformation and extraction of morphine by the liver are complete but the rate-limiting step for morphine elimination is its reuptake of the drug from peripheral tissues. The effect of enflurane–nitrous oxide anesthesia on the elimination of morphine from plasma appears to have been minimal, but a definite conclusion on this point awaits studies of morphine kinetics in awake and anesthetized volunteers.

APPENDIX

After intravenous injection, the decline of unchanged morphine concentrations in plasma was triphasic, and could be fitted to an exponential time function using the method of residuals as described by Gibaldi and Perrier[7] and modified for use as a computer program. The equation is as follows:

¶ The commercially available antibody used in some studies[14,15] is equally reactive with morphine and morphine-glucuronide.

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$$C_{p(t)} = P \exp^{-\pi t} + A \exp^{-\alpha t} + B \exp^{-\beta t}$$

where

$C_{p(t)}$ = the concentration of morphine in plasma at time t;
P, A, B = the extrapolated zero intercepts computed from least-squares analysis of the data;
π, α, β = the first-order rate constants.

The apparent volume of distribution (V_d), the apparent volume of the central compartment (V_1), and the total-body clearance (Cl_B) were calculated by the following formulas:

$$V_d = \frac{\text{dose}}{AUC^* \cdot \beta}$$

$$V_1 = \frac{\text{dose}}{C_{p(0)}}$$

$$Cl_B = \frac{\text{dose}}{AUC}$$

$$AUC^* = \frac{P}{\pi} + \frac{A}{\alpha} + \frac{B}{\beta}$$

$$C_{p(0)} = P + A + B$$

The pharmacokinetics of morphine can be represented by a three-compartment model (fig. 2).[7] Intravenous morphine is introduced directly into plasma which is part of the central compartment. Morphine presumably is eliminated from the body by way of the central compartment at a rate (k_{10}) determined primarily by biotransformation in the liver and to a lesser degree by renal excretion of the unchanged drug.[10] Both liver and kidney are well perfused tissues and are assumed to be in the central compartment. Morphine is also distributed to two other groups (compartments) of tissues at different rates (k_{12}, k_{13}), probably reflecting differences in tissue perfusion. The rates of return of morphine from these two peripheral compartments are represented by k_{21} and k_{31}. The ultimate elimination of morphine from the peripheral compartments is assumed to occur by way of the central compartment containing the organs of elimination.

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* AUC is the area under the plasma concentration *vs.* time curve.

References

1. Brunk SF, Delle M: Morphine metabolism in man. Clin Pharmacol Ther 16:51–57, 1974
2. Berkowitz BA, Ngai SH, Yang JC, et al: The disposition of morphine in surgical patients. Clin Parmacol Ther 17: 629–635, 1975
3. Stanski DR, Greenblatt DJ, Lappas DG, et al: Kinetics of high-dose intravenous morphine in cardiac surgery patients. Clin Pharmacol Ther 19:752–756, 1976
4. Stanski DR, Greenblatt DJ, Lowenstein E: Kinetics of intravenous and intramuscular morphine. Clin Pharmacol Ther 24:52–59, 1978
5. Dahlström B, Bolme P, Feychting H, et al: Morphine kinetics in children. Clin Pharmacol Ther 26:354–365, 1979
6. Woods LA, Cochin J, Fornefeld EG, et al: Estimation of morphine in biological materials. J Pharmacol Exp Ther 111:64–73, 1954
7. Gibaldi M, Perrier D: Pharmacokinetics. New York, Marcel Dekker, Inc., 1975, pp 281–292
8. Murphy MR, Olson WA, Hug CC: Pharmacokinetics of ^{3}H-fentanyl in the dog anesthetized with enflurane. Anesthesiology 50:13–19, 1979
9. Boxenbaum HG, Riegelman S, Elashoff RM: Statistical estimations in pharmacokinetics. J Pharmacokinet Biopharm 2:123–148, 1974
10. Way EL, Adler TK: The pharmacologic implications of the fate of morphine and its surrogates. Pharmacol Rev 12: 383–446, 1960
11. Goldberg AH: Anesthesia and hepatic blood flow. Int Anesthesiol Clin 8:315–327, 1970
12. Yang JC, Clark WG, Ngai SH, et al: Analgesic action and pharmacokinetics of morphine and diazepam in man. Anesthesiology 51:495–502, 1979
13. Catlin DH: Pharmacokinetics of morphine by radioimmunoassay: The influence of immunochemical factors. J Pharmacol Exp Ther 200:224–235, 1977
14. Johnstone RE, Jobes DR, Kennell EM, et al: Reversal of morphine anesthesia with naloxone. Anesthesiology 41: 361–367, 1974
15. Lappas DG, Geha D, Fischer JE, et al: Filling pressures of the heart and pulmonary circulation of the patient with coronary artery disease after large intravenous doses of morphine. Anesthesiology 42:153–159, 1975
16. Mule SJ, Woods LA: Distribution of N-^{14}C-methyl labeled morphine. I. In central nervous system of nontolerant and tolerant dogs. J Pharmacol Exp Ther 136:232–241, 1962
17. Hug CC Jr, Murphy MR, Rigel EP et al: Pharmacokinetics of morphine injected intravenously into the anesthetized dog. Anesthesiology 54:38–47, 1981
18. McClain DA, Hug CC Jr: Intravenous fentanyl kinetics. Clin Pharmacol Ther 28:106–114, 1980
19. Hug CC Jr, Murphy MR: Fentanyl disposition in cerebrospinal fluid and plasma and its relationship to ventilatory depression in the dog. Anesthesiology 50:342–349, 1979

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