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Pharmacokinetics of Fentanyl in Patients Undergoing Abdominal Aortic Surgery

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The authors determined the pharmacokinetics of fentanyl 100 $\mu g \cdot kg^{-1}$ iv in patients undergoing elective abdominal aortic surgery. The mean (±SD) age of the ten patients was 67.2 ± 8.7 yr; their mean weight was 78.5 ± 13.7 kg. Seven patients had aortic aneurysm repair, and the other three patients had aortobifemoral grafts. Serum fentanyl concentrations were determined from samples drawn at increasing intervals over a 24-h period. A three-compartment pharmacokinetic model was fit to the concentration *versus* time data. Total drug clearance was 9.8 ± 1.8 $ml \cdot min^{-1} \cdot kg^{-1}$. The volume of distribution at steady-state (V_{dss}) was 5.4 ± 1.9 · 1 kg^{-1}. Elimination half-time was 8.7 ± 2.5 h. There were no significant correlations between these pharmacokinetic parameters and patient's age, duration of aortic cross-clamping, duration of surgery, intraoperative blood loss, or volume of iv fluids given intraoperatively. In healthy volunteers or patients undergoing general surgery, other investigators report mean elimination half-times for fentanyl ranging from 1.7 to 4.4 h. The prolonged elimination half-time in patients having abdominal aortic surgery has important clinical implications. In particular, recovery from large doses will take much longer than would have been anticipated from previously published fentanyl pharmacokinetic data. (Key words: Analgesics, narcotic: fentanyl. Anesthetics, intravenous: fentanyl. Pharmacokinetics: fentanyl. Surgery: vascular; aorta).

FENTANYL–OXYGEN ANESTHESIA is widely used for patients having coronary artery bypass grafting. Advantages of this anesthetic technique include minimal cardiovascular depression and blunting of endocrine and hemodynamic responses to noxious stimuli.[1] These advantages suggest that high-dose fentanyl might be a useful anesthetic in patients having abdominal aortic surgery. Ideally, dosing regimens should be based on pharmacokinetic data and principles to help avoid both inadequate and excessive doses. Pharmacokinetic data are also required to develop infusion regimens for achieving and maintaining a desired drug concentration. Accordingly, we determined the pharmacokinetics of fentanyl 100 $\mu g \cdot kg^{-1}$ in this patient population.

Methods

Ten patients (nine men, one woman) undergoing elective abdominal aortic surgery with infrarenal aortic cross-clamping were studied. Their mean (±SD) age was 67.2 ± 8.7 yr, and their mean weight was 78.5 ± 13.7 kg. Seven patients underwent aortic aneurysm repair, and three had aortobifemoral grafts. The study was approved by the Human Subjects Committee, and informed consent was obtained from each patient.

The patients' regular medications were continued up to and including the day of surgery (table 1). Morphine 0.1 $mg \cdot kg^{-1}$ im and scopolamine 0.006 $mg \cdot kg^{-1}$ im were given 1 h prior to surgery. Intravenous, radial arterial, and pulmonary arterial catheters were inserted before induction of anesthesia. Anesthesia was induced with fentanyl 100 $\mu g \cdot kg^{-1}$ iv over 2 min, preceded by metocurine 0.1 $mg \cdot kg^{-1}$ iv and pancuronium 0.025 $mg \cdot kg^{-1}$ iv. Four patients (subjects 1, 3, 4, and 9) also received lidocaine 1.5 $mg \cdot kg^{-1}$ iv after the fentanyl injection. Ventilation was controlled manually, and the trachea was intubated 4 min after the fentanyl infusion. Other anesthetic drugs given at the discretion of the attending anesthesiologist were diazepam 2.5–10 mg iv and, only after removal of the aortic cross-clamp, nitrous oxide 50% to 70% (table 1). Fluid therapy consisted of replacement of the measured blood loss with an appropriate volume of packed red blood cells plus sufficient crystalloid to maintain pulmonary artery wedge pressure near the control value. Changes of heart rate or mean arterial pressure of greater than 20% of awake control values were treated with appropriate vasoactive drugs (table 1). Neuromuscular blockade was maintained with additional small doses of metocurine and pancuronium (4:1 mixture).

Intravenous medications given during the first 24 h postoperatively are shown in table 1. Fluids were infused as necessary to maintain normal filling pressures and urine output. The patterns were electively ventilated overnight and extubated 17 to 30 h from the time of induction of anesthesia, except for subject 6, who developed respira-

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tory failure and required mechanical ventilation for 96 h.

After the fentanyl infusion, samples of arterial blood were withdrawn according to the following schedule: 1, 3, 5, 10, 15, 20, 30 45, 60, 90 min and 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24 h. The serum was separated and stored at −20° C.

Analytic Techniques

Serum fentanyl concentrations were determined by gas–liquid chromatography with a nitrogen–phosphorous detector. After adding 0.1 ml of alfentanil solution (200 $ng \cdot ml^{-1}$) as the internal standard to 1.0 ml serum, the samples were alkalinized with 0.1 ml 1N NaOH and extracted into 5 ml hexane. The organic fraction was evaporated under dry air and reconstituted with 8 μl hexane. Three to 5 μl were then injected onto a 15 m × 0.32 mm fused silica capillary column (DB-1, J and W Scientific). The oven temperature was programmed to increase from 150° C to 260° C at 30° $C \cdot min^{-1}$. The injector and detector were kept at 310° C. The detection limit of the assay was 0.3 $ng \cdot ml^{-1}$. The coefficient of variation averaged 6.8% over the concentration range 5 to 100 $ng \cdot ml^{-1}$ and was 20.5% at 1 $ng \cdot ml^{-1}$.

The serum fentanyl concentrations were greater than 5 $ng \cdot ml^{-1}$ for the first 8 to 10 h. In one patient the samples drawn at 20 and 24 h had less than 1 $ng \cdot ml^{-1}$ fentanyl, as did the final sample from another patient. These three data points were excluded from the pharmacokinetic analysis.

Data Analysis

Biexponential and triexponential equations were fit to the serum fentanyl concentration *versus* time data using extended least squares[2] nonlinear regression.¶ The statistically preferred model (two- or three-compartment) for each patient was determined by comparison of log-likelihood values¶ of the polyexponential equation.

After correction for the 2-min infusion,[3] standard formulas were used to calculate distribution and elimination half-times, volume of the central compartment (V_c), volume of distribution at steady-state (V_{dss}), and total drug clearance.[4] Linear regressions of the derived pharmacokinetic parameters on various clinical factors (age, duration of surgery, duration of abdominal aortic cross-clamping, estimated blood loss, and total volume of colloid and crystalloid infused intraoperatively) were performed.

¶ Sheiner LB: ELSFIT: A program for extended least squares fit to individual pharmacokinetic data. Users Manual. Department of Laboratory Medicine, M523, University of California, San Francisco, California 94143.

TABLE 1. Perioperative Drug Therapy

Subject	Regular Medications	Intraoperative Medications	Postoperative (first 24 h) Medications
1	l-Thyroxine	SNP Propranolol Diazepam Mannitol	SNP Propranolol
2	Propranolol Hydrochlorothiazide	NTG	Propranolol Diazepam Morphine
3	Propranolol	Hydralazine SNP Nitrous oxide	Propranolol SNP Diazepam
4	Propranolol	Diazepam SNP NTG Nitrous oxide Mannitol	Diazepam SNP Propranolol Lidocaine Morphine
5	Propranolol	Hydralazine	Propranolol Morphine Dopamine
6	Metoprolol Hydralazine	Mannitol	Phenylephrine Diazepam Morphine Furosemide Mannitol Dopamine
7	Methyldopa Hydrochlorthiazide Salbutamol Aminophylline	Mannitol SNP NTG	Methyldopa SNP NTG Dopamine
8		Diazepam SNP NTG Propranolol	Diazepam SNP NTG
9	Propranolol Chlorthalidone	SNP Diazepam Mannitol	Propranolol SNP Diazepam Morphine
10		Diazepam Propranolol Mannitol SNP	Morphine Propranolol Hydralazine SNP

SNP = sodium nitroprusside; NTG = nitroglycerin.

Results

The pharmacokinetic parameters are presented in tables 2 and 3. In all ten subjects, the three-compartment model was statistically preferred to the two-compartment model. Linear regression analyses of clearance, V_{dss}, and elimination half-time against each of age, duration of aortic cross-clamping, duration of surgery, blood loss, and total volume of iv fluids given intraoperatively revealed no significant associations (table 4).

Figure 1 shows the triexponential serum fentanyl concentration *versus* time curve for the patient whose elimi-

TABLE 2. Pharmacokinetic Variables

Subject	Weight (kg)	Clearance (ml · min^{-1} · kg^{-1})		
		Total Drug Clearance	Rapid Intercompartmental Clearance	Slow Intercompartmental Clearance
1	80.5	12.0	76.1	23.4
2	86.3	7.0	31.2	13.2
3	63.0	8.4	23.7	13.5
4	67.0	11.8	74.8	38.9
5*	59.1	10.9	50.6	18.7
6	86.4	11.1	14.9	31.6
7	89.8	9.1	22.2	12.7
8	80.0	8.2	76.2	20.0
9	103.0	8.1	30.0	20.6
10	70.0	11.1	138.9	13.2
Mean ± SD	78.5 ± 13.7	9.8 ± 1.8	53.9 ± 38.3	20.6 ± 8.8

* Female subject.

nation half-time was closest to the mean. The measured serum fentanyl concentrations demonstrate an apparent secondary peak approximately 6 h after injection. Such peaks (defined as an increase in two consecutive samples of the measured fentanyl concentration of at least twice the coefficient of variation of the assay at that concentration) occurred in three subjects 5 to 8 h after the fentanyl injection. At this time the patients were in the intensive care unit and were beginning to move about spontaneously as the effects of anesthetic and neuromuscular blocking drugs dissipated.

Discussion

The pharmacokinetics of fentanyl in our patients undergoing abdominal aortic surgery are very different from previous determinations of fentanyl pharmacokinetics in normal volunteers or patients having nonvascular surgery.[5] Total drug clearance in our patients was 9.8 ± 1.8 ml · min^{-1} · kg^{-1} compared with previously reported mean values ranging from 12.6 to 15.5 ml · min^{-1} · kg^{-1}. We found the V_{dss} to be 5.4 ± 1.9 · 1 kg^{-1} compared to mean values of 3.4 to 3.8 · 1 kg^{-1}. The elimination half-time of any drug is inversely proportional to its clearance and directly proportional to its volume of distribution. In our patients, both these factors contributed to an elimination half-time of 8.7 ± 2.5 h, which is much longer than other reported mean values of 1.7 to 4.4 h.[5] The mean elimination half-time in our patients was also longer than the mean elimination half-time reported in two studies of fentanyl disposition after cardiopulmonary bypass (8.7 h *versus* 5.2 h[6] and 7.0 h[7]). Unfortunately, clearance and V_{dss} could not be determined for the patients having cardiac surgery, making additional comparisons impossible.

Many factors could explain altered drug disposition in patients having abdominal aortic surgery. These patients are elderly and have pre-existing cardiovascular disease. Intraoperative events such as aortic cross-clamping and fluid shifts could also affect drug distribution and elimination.

Our patients' ages ranged from 55 to 80 yr. Linear regression analyses indicated that age did not significantly affect total drug clearance, V_c, V_{dss}, or elimination half-time. Bentley *et al.* studied the effect of age on fentanyl disposition in patients having intraabdominal surgery.[8] The mean elimination half-time in their four elderly subjects (mean age 67) was 15.8 h *versus* 4.4 h in 5 control patients (mean age 36). This was attributed to decreased fentanyl clearance in the elderly, 4.0 ml · min^{-1} · kg^{-1} *versus* 15.4 ml · min^{-1} · kg^{-1}. Their data may be unreliable because the duration of blood sampling, 7 h, was less than one-half the estimated elimination half-time in their el-

TABLE 3. Pharmacokinetic Variables (Continued)

Subject	Volumes (l kg^{-1})				Half-times		
	V_c	V_2	V_3	V_{dss}	$T\frac{1}{2}\alpha$ (min)	$T\frac{1}{2}\beta$ (min)	$T\frac{1}{2}\gamma$ (h)
1	0.449	1.00	4.20	5.65	2.3	30.3	7.1
2	0.088	0.50	3.44	4.03	1.1	28.0	9.4
3	0.111	0.30	2.48	2.90	1.5	19.3	5.9
4	0.186	0.26	3.33	3.78	0.8	7.1	4.6
5*	0.420	1.72	5.99	8.12	3.3	60.8	11.6
6	0.438	0.59	6.57	7.60	4.9	36.6	10.1
7	0.165	0.31	3.00	3.48	2.3	21.4	6.9
8	0.266	0.75	5.28	6.29	1.5	27.5	11.5
9	0.165	0.30	3.92	4.38	1.7	15.4	8.3
10	0.554	1.76	5.22	7.54	1.9	63.6	11.5
	0.285 ± 0.166†	0.75 ± 0.57	4.34 ± 1.36	5.38 ± 1.92	2.1 ± 1.2	31.0 ± 18.4	8.7 ± 2.5

V_c = volume of the central compartment; V_2 = volume of the rapidly equilibrating peripheral compartment; V_3 = volume of the slow equilibrating peripheral compartment; V_{dss} = volume of distribution at steady-state (the sum of V_c, V_2, and V_3 may not equal V_{dss} because of rounding off); $T\frac{1}{2}\alpha$ = rapid distribution half-time; $T\frac{1}{2}\beta$ = slow distribution half-time; $T\frac{1}{2}\gamma$ = elimination half-time.

* Female subject.

† Mean ± SD.

TABLE 4. Results of Regression Analyses

Independent Variables (mean ± SD)	Dependent Variables							
	V_c		V_{dss}		Clearance		Elimination Half-time	
	r	P	r	P	r	P	r	P
Age (67.2 ± 8.7 yr)	−0.56	0.10	−0.47	0.17	−0.48	0.17	−0.29	0.45
Duration of cross-clamping (84 ± 25 min)	−0.06	>0.5	0.10	>0.5	0.12	>0.5	−0.02	>0.5
Duration of surgery (220 ± 59 min)	−0.27	0.47	−0.07	>0.5	−0.04	>0.5	−0.09	>0.5
Estimated blood loss (720 ± 422 ml)	0.17	>0.5	0.17	>0.5	0.15	>0.5	0.33	0.39
Total volume of iv fluids (6270 ± 1726 ml)	0.23	>0.5	0.45	0.19	−0.09	>0.5	0.53	0.12

V_c = volume of the central compartment; V_{dss} = volume of distribution at steady-state; Clearance = total drug clearance.

derly patients, 15.8 h. In contrast, Cartwright *et al.* did not find any age-related changes in fentanyl pharmacokinetics in 24 patients aged 39 to 72 yr.[9] These discrepancies clearly indicate that the effect of age on fentanyl disposition deserves further study.

Abdominal aortic cross-clamping might alter the distribution and elimination of fentanyl. Infrarenal aortic cross-clamping activates the renin–angiotension system,[10] which could decrease mesenteric and hepatic blood flow.[11] However, we could not find significant correlations between the derived pharmacokinetic variables (clearance, V_{dss}, and elimination half-time) and either the duration of aortic cross-clamping or the duration of surgery.

Dilution of plasma with crystalloid has been shown to decrease binding of fentanyl to plasma proteins.[12] The resultant increase in the free fraction of fentanyl will tend to increase the V_{dss}.[13] The large volumes of fluids given to our patients could have contributed to the large V_{dss} we observed. However, the pharmacokinetic variables were not significantly correlated with the total volume of iv fluids given intraoperatively. Before dismissing these factors as being unimportant, we must emphasize that our study was not specifically designed to examine their roles and that our group of patients was relatively small and homogeneous. Accordingly, demonstration of significant correlations would not be expected. The influence of these factors can only be determined adequately by additional prospective studies.

Most of our patients received propranolol in the perioperative period. Propranolol can reduce hepatic blood flow and has been shown to slightly decrease clearance of other drugs metabolized by the liver.[14] The values for fentanyl clearance in those who did not receive propranolol were within the range of clearances in those who were on propranolol (tables 1 and 2). This suggests that propranolol therapy was not a major factor.

Two aspects of our study design were very different from previous studies of fentanyl pharmacokinetics. First, our dose was 100 $\mu g \cdot kg^{-1}$, whereas other investigators gave 10 $\mu g \cdot kg^{-1}$ or less. Murphy *et al.*[15] have shown that the pharmacokinetics of fentanyl in the dog are independent of dose over the range of 6.4 $\mu g \cdot kg^{-1}$ to 640 $\mu g \cdot kg^{-1}$. This has not been confirmed in human subjects, but it makes it unlikely that the larger dose we gave is solely responsible for the differences between our results and previously published reports. Second, we collected our final blood sample 24 h after the fentanyl injection

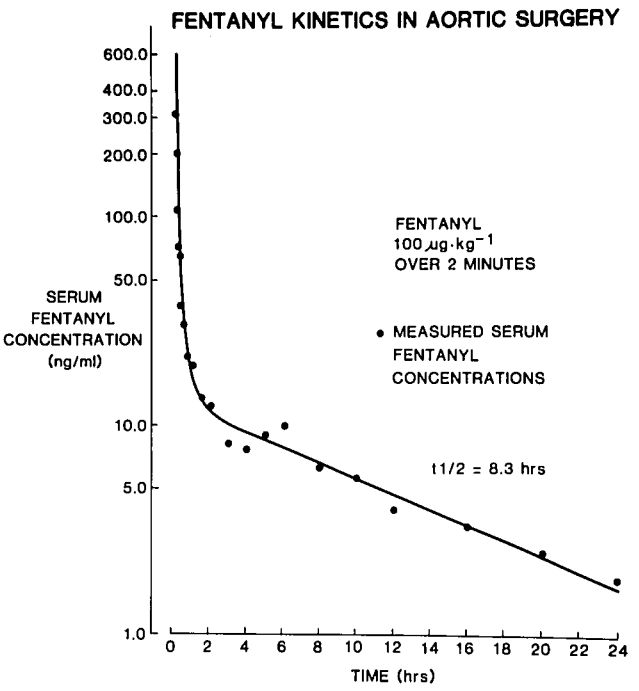

FIG. 1. A representative serum fentanyl concentration *versus* time curve. The measured concentrations demonstrate a secondary peak at approximately 6 h. The line adjacent to the symbols is the triexponential function fit to the data by nonlinear regression.

and, thus, had more than 20 h of elimination-phase data. The duration of blood sampling in previous studies has been 8 h or less.[5] The magnitude of the elimination half-time may be underestimated if the duration of sampling does not extend far enough into the elimination phase.[16] This difference in study design could account for some of the differences between our results and other reports. We tested this hypothesis by truncating the concentration *versus* time data sets to 12 h and repeating the pharmacokinetic analyses. In seven of the ten patients, truncation of the data yielded estimates of elimination half-times that were shorter, with clearance increasing and V_{dss} decreasing. The parameter estimates were unaffected by truncation in one subject. In the remaining two subjects, the presence of secondary peaks resulted in gross overestimation of the elimination half-time. The observed differences between the pharmacokinetic parameters obtained from the full (24-h) and truncated (12-h) data sets were rendered statistically insignificant by these two discordant subjects. A study of fentanyl pharmacokinetics in general surgical patients in which blood sampling was also continued for 24 h has recently been published.[17] It is noteworthy that the mean elimination half-time in that study, 9.4 h, was very close to the elimination half-time of 8.7 h observed in our patients.

Secondary peaks of the measured fentanyl concentration during the elimination phase have been observed by several investigators.[8,12,18,19] In three of our patients, secondary peaks occurred approximately 6 h after the fentanyl injection. These secondary peaks were coincident with the onset of spontaneous motor activity as the patients recovered from anesthesia and neuromuscular blockade. Skeletal muscle is a major storage depot for fentanyl.[20] The association of secondary peaks with increased muscle activity is consistent with the hypothesis that fentanyl is eluted from muscle tissue by exercise-induced increases of regional blood flow.[5,12] Fortunately, as shown in figure 1, the triexponential model was able to approximate closely the concentration *versus* time data in spite of secondary peaks.

Our results have important clinical implications. Ventilatory depression appears to be directly related to serum fentanyl concentration.[19,21] If patients undergoing abdominal aortic surgery are given large doses of fentanyl, recovery will take much longer than would have been anticipated from previous studies of fentanyl pharmacokinetics in patients undergoing general or cardiac surgery.

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