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A Review of the Use of Fentanyl Analgesia in the Management of Acute Pain in Adults

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FENTANYL was one of a series of opioids synthesized by Janssen Pharmaceutica in the 1950s and 1960s in an effort to produce opioid analgesics with enhanced analgesic activity and potency and fewer adverse effects compared with morphine or meperidine.[1,2] It was first used clinically as a component of neuroleptanalgesia in combination with the butyrophenone, droperidol.[3] Between 1975 and 1981, fentanyl was adopted widely as a potent intraoperative analgesic agent with relatively few adverse effects. In small-to-moderate bolus doses (3 to 5 μg/kg), it combined with different intravenous supplements to produce "balanced" anesthesia,[4] whereas large doses (as much as 100 μg/kg) were used to induce and to maintain anesthesia in critically ill patients and those undergoing cardiopulmonary bypass procedures.[5]

Fentanyl's popularity as an intraoperative agent relates directly to the cardiovascular stability it provides, even in critically ill patients.[6,7] But its analgesic efficacy relative to the intensity of side effects prompted much interest in its use as an analgesic agent after operation or in the intensive care unit. Investigators began by exploring alternatives to the traditional intramuscular or intravenous routes for postoperative administration to optimize the potential clinical benefits of fentanyl's physiochemical properties. This article reviews the literature related to the use of fentanyl as an analgesic in the postoperative period and in patients in the intensive care unit, and it evaluates the pharmacokinetics, pharmacodynamics, efficacy, and limitations of existing and experimental routes of administration.

Physical and Chemical Properties of Fentanyl

Fentanyl, N-(1-phenethyl-4-piperidyl) propionanilide, is structurally related to meperidine. Commercially, fentanyl is formulated as a citrate, available in a water-soluble, white crystalline powder that requires no preservatives. It has a molecular weight of 528.29 and a melting point of 148.5 to 150°C. Each milliliter of aqueous solution contains a base of 0.05 mg fentanyl (0.0785 mg of the citrate).

The negative logarithm of the acid ionization constant of fentanyl (pKa) is 8.43. At physiologic *p*H, 8.5% of the compound is un-ionized in plasma and 84% is bound to erythrocytes, α_1-acid glycoprotein, and plasma albumin.[8] The octanol-water partition coefficient at physiologic *p*H is 816 for fentanyl compared with 1.4 for morphine. Therefore, fentanyl is highly lipophilic, whereas morphine is hydrophilic. Multiplying this partition coefficient by the plasma-free fraction (table 1) yields a relative potential to enter the central nervous system that is approximately 133 times larger than that of morphine.[9]

Optimization of the molecular configuration of fentanyl increased its potency. Fentanyl is 100 to 300 times more potent than morphine per dose, depending on the animal species.[10–12] This greater dose potency permits a low therapeutic blood concentration of approximately 0.6 to 3 ng/ml for analgesia. This, in turn, necessitates a sensitive method of assay.

Radioimmunoassay and gas liquid chromatography are the two most common methods used. The current radioimmunoassay method can measure plasma fentanyl concentrations as low as 0.06 ng/ml and was first reported in 1977.[13] The standard curves are linear for a concentration range of 0.06–20 ng/ml, and the coefficient of variation of the assay ranges from 1–12%.[14–21]

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Table 1. Pharmacology Comparison between Fentanyl and Morphine in Adults

	Morphine	Fentanyl
Rapid distribution half-life ($t_{1/2}$ π, min)	1.2–2.5	1.0–1.7
Slow distribution half-life ($t_{1/2}$ α, min)	9–13.3	13–28
Elimination half-life ($t_{1/2}$ β, h)	1.7–2.2	3.1–7.9
Blood-brain equilibration half-life ($t_{1/2}$ k_{eo}, min)	15–20	6.6
Volume of distribution, steady state (L/kg)	3.2–3.4	3.2–5.9
Clearance* ($ml \cdot kg^{-1} \cdot min^{-1}$)	15–23	8–21
pK_a	7.93	8.43
% unionized at *p*H 7.4	23	8.5
Octanol: H_2O partition coefficient	1.4	816
% unbound drug at *p*H 7.4	70	16
Relative CNS penetrability†	1	133

* Calculated from blood level measured in plasma.

† Apparent octanol: H_2O partition coefficient at *p*H 7.4 multiplied by the free fraction of drug in plasma and divided by the value (0.98) for morphine gives the relative potential of the drug to enter the CNS.

Adapted and modified from Murphy,[189] Hug,[9] with permission; $t_{1/2}k_{eo}$ data from Inturrisi,[190] Scott.[32]

However, radioimmunoassay analysis can overestimate plasma fentanyl concentrations (fentanyl C_P) by as much as 29 to 100%,[22] limiting reliability, and thereby contributing to the observed differences in the pharmacokinetic data reported for fentanyl.[22]

Assay by gas liquid chromatography using either flame-ionization, nitrogen phosphorus, or mass spectrometric detection is sensitive and reproducible. With nitrogen phosphorus,[23] the mean coefficient of variation for concentrations ranging from 0.25–10 ng/ml is 4.65%; with mass spectrometric detection, the mean coefficient of variation is 6.9% for a range of 0.2–68 ng/ml.[24] When compared directly with the radioimmunoassay method, the gas liquid chromatography–nitrogen phosphorus method results in comparable values in the spiked control and patient samples.[25] At the detection limit of 0.25 ng/ml, gas liquid chromatography has a coefficient of variation of 14.7%, comparable to 14.2% for radioimmunoassay. At higher concentrations, the coefficient of variation decreases to approximately 5%. This increased variability at the detection limit significantly affects pharmacokinetic analysis, because the terminal half-life for low-to-moderate doses of fentanyl (5–15 μg/kg) is estimated using serum levels in the region of this limit. Accordingly, limitations of the assay, whether radioimmunoassay or gas liquid chromatography, must be considered in interpreting studies that profile fentanyl pharmacokinetics.

Fentanyl has both high lipid solubility and a pattern of rapid and extensive redistribution, making it an ideal agent to evaluate drug delivery systems and routes of administration other than the traditional parenteral routes. Consequently, it has been administered *via* intramuscular, intravenous (bolus injection, infusion, patient-controlled analgesia [PCA]), neuraxial (epidural, intrathecal), transdermal, transmucosal (oral or intranasal), and inhalational routes.

Systemic Administration: Intravenous

Pharmacokinetics

After an intravenous bolus, fentanyl distributes rapidly from plasma to highly vascular tissues (heart, lung, and brain). More than 80% of the injected dose leaves plasma in less than 5 min,[26] and 98.6% leaves by 1 h.[27] Elimination from the vascular tissue also is rapid as fentanyl redistributes to other sites, such as muscle and fat.[28] In rats, fentanyl C_P peaks in muscle 5 min after a bolus dose, and in fat at approximately 30 min (fig. 1). Removal from muscle and fat is slower than uptake, because both tissues act as storage sites; in muscle this is because of its mass, and in fat because of the high lipid solubility of fentanyl.[29] After initial equilibration with adipose tissue, fentanyl C_P decreases, and then fat slowly releases the fentanyl back into the plasma. This slow release results in a lengthy elimination half-time of 3.1 to 7.9 h (table 1). Thus, fentanyl's short duration of action after a single dose results from redistribution rather than elimination. After large or multiple smaller doses, fentanyl accumulates as a result of its long half-time, and redistribution is less effective in removing fentanyl from its site of action in the brain.[9,30]

Fentanyl is metabolized almost exclusively in the liver to norfentanyl, hydroxy-proprionyl-fentanyl, and hydroxyproprionyl-norfentanyl.[31] The pharmacologic activity of fentanyl metabolites is unknown but is believed to be minimal.[31] Less than 10% of fentanyl is excreted unchanged by the kidney.[27] The total body clearance of fentanyl is high, between 8 and 21 $ml \cdot kg^{-1} \cdot min^{-1}$, and approaches that of liver blood flow, reflecting the high hepatic extraction ratio. The high lipid solubility of fentanyl contributes to a large volume of distribution (3.2–5.6 l/kg).

Pharmacodynamics

Several studies correlate fentanyl C_P with analgesia (the desired effect) and respiratory depression (the most dangerous side effect). However, the intensity of fenta-

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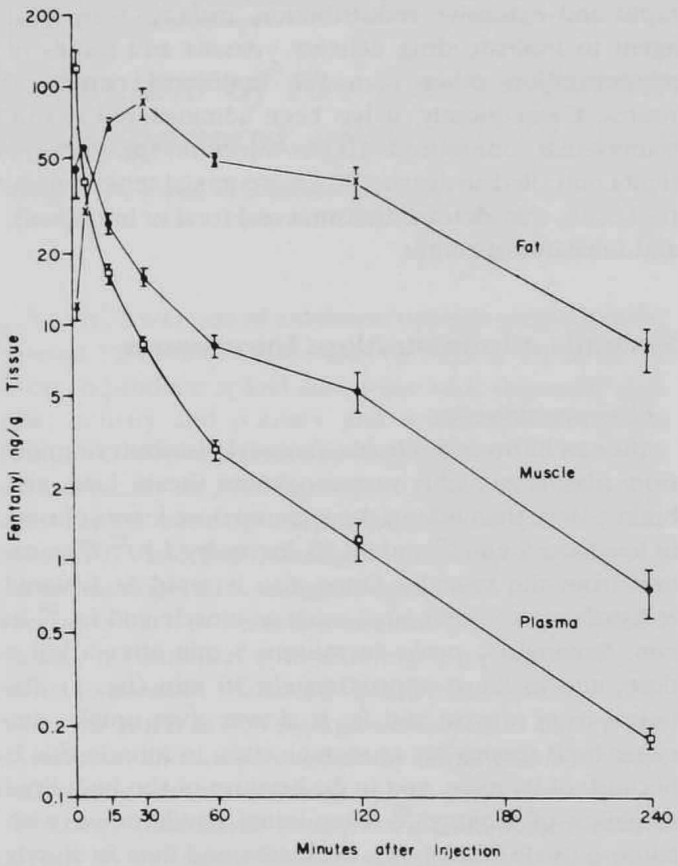

Fig. 1. Concentrations of unchanged fentanyl in muscle, fat, and plasma after an intravenous injection of 50 μg/kg in six rats. Each data point represents the mean ± SEM. Reprinted with permission.[28]

nyl's effect correlates with the drug concentration at the site of action (effect site) and not necessarily the plasma concentration. For opioids, the effect site or biophase is the opioid receptor in the brain and spinal cord. Additional time is needed for fentanyl to cross the blood-brain barrier to reach the effect site. The temporal lag between plasma concentration and the effect on the biophase is called hysteresis. A first-order rate constant (k_{eo}) characterizes the temporal aspects of equilibration between the effect-compartment concentration and the serum concentration. Thus, the half-time for equilibration $t_{1/2}k_{eo}$ ($0.693/k_{eo}$) quantifies the magnitude of the hysteresis (table 1). Using electroencephalography to measure opioid effect, one group of investigators found a 3- to 5-min lag between increasing fentanyl C_P and electroencephalography slowing during a 5-min fentanyl infusion.[32] After the infusion was discontinued, resolution of electroencephalography changes lagged behind decreasing fentanyl C_P by 10 to 20 min (fig. 2).

Different modes of administration have different degrees of hysteresis. With a rapid change in plasma concentration (*e.g.*, after an intravenous bolus), the temporal lag will be greatest; with a slow change in concentration (*e.g.*, with a steady continuous infusion), the lag will be smallest. Consequently, pharmacodynamic data obtained *via* different modes must be compared with caution.

Plasma Fentanyl Concentration and Analgesia. Most studies correlating fentanyl C_P with its analgesic and side effects have estimated plasma fentanyl from gradually changing concentrations in selected groups of patients. Data from studies limited primarily to patients receiving intravenous fentanyl for postoperative analgesia indicate a mean analgesic C_P ranging from 0.6–3 ng/ml.[14,15,17,18,33–38] Infusion of fentanyl to achieve a steady state C_P is reported in one study[14] to produce "slight but significant analgesia" at a mean concentration of 0.6 ng/ml and "significantly greater analgesia" at a C_P of 1.7 ng/ml, and, in another,[35] an analgesic range of 1–3 ng/ml. With PCA, the mean minimum effective analgesic concentration (MEC—fentanyl C_P immediately before the patient administers the next bolus dose[37]) has been reported as 1.35 ng/ml,[15] 1.54 ng/ml,[36] and 0.63 ng/ml.[37] Thus, mean MEC values range from 0.6–1.54 ng/ml, whereas values for individual patients range from 0.2–8.0 ng/ml with a log-normal distribution.[15]

Studies correlating fentanyl C_P with analgesic effect *via* visual analog pain scale ([VAS] 0 = no pain, 10 = maximum pain) scores report that the mean fentanyl C_P of 0.3 to 0.7 ng/ml and 0.5 to 1.2 ng/ml during PCA correlate with VAS scores at rest of 3 or 4[19] and 2 to 4,[16] respectively. Scores of 1 to 3 are associated with a C_P of 1 or 2 ng/ml in different postoperative patient populations (thoracotomy,[17,18] cesarean section,[38] knee sur-

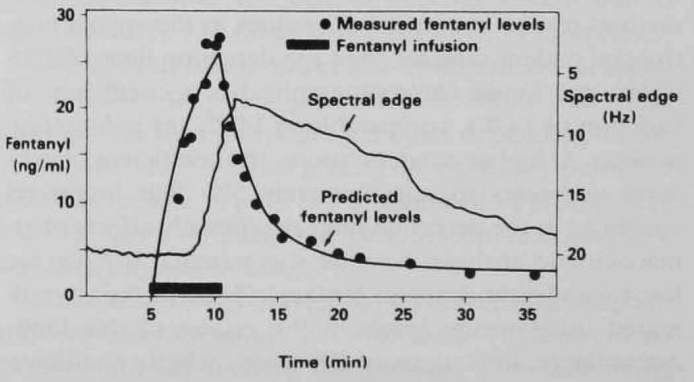

Fig. 2. The time course of the electroencephalogram spectral edge and serum fentanyl concentrations. The spectral edge axis is inverted. The electroencephalogram spectral edge changes lag behind the changes in serum concentration. Fentanyl infusion rate = 150 μg/kg (solid bar). Reprinted with permission.[32]

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gery[39]) treated by a bolus dose plus infusion of fentanyl. However, measurements of the C_p associated with effective analgesia often are obtained while patients are at rest; at a similar C_p, VAS scores markedly increase with movement or coughing.[39]

The observed variability in the analgesic C_p reported for fentanyl in large part is caused by differences in study design and in individual pharmacodynamic responses. Analgesic requirements of individual patients and different surgical populations vary over a sixfold range for fentanyl and other opioids.[15,37,40] With respect to study design, the residual presence of anesthetic drugs and possible coadministration of central nervous system depressants affect the relation between doses or the C_p of fentanyl and the intensity of analgesia and side effects. The degree of drug interaction also varies by study design. The types of surgical procedure also alter the degree of postoperative pain, and thereby the analgesic requirement: With a similar study design, we would expect a higher analgesic requirement in patients undergoing thoracotomy than hysterectomy. Different measurements of analgesic effect are used, including descriptive terms,[14] MEC,[37] C_p associated with 50% reduction in pain intensity,[33] and VAS score.[17–19,38] The timing of blood sampling also differs: Some investigators sample at predetermined intervals, correlating these results with analgesic effect,[38] whereas others measuring MEC sample just before the patient administers the next bolus.[15,36,37]

Intravenously administered fentanyl produces effective analgesia in patients after operation at C_p values ranging from 0.6–3.0 ng/ml. Pain control at rest is satisfactory within this range, but the analgesic effect diminishes with movement or coughing,[39] suggesting that a higher C_p may be required if analgesia is intended to promote either of these responses.

Plasma Fentanyl Concentration and Respiratory Depression. Studies investigating the connection between fentanyl C_p and ventilatory effect show a concentration–effect relation.[33,41,‡] With intravenous bolus elimination, a C_p of 3 or 4 ng/ml produces a 50% decrease in the slope of minute ventilation (V_E) *versus* end-tidal carbon dioxide concentration.[20,21,42] However, these measured plasma concentrations may not reflect effect-site concentrations of fentanyl, as a result of the hysteresis between these values with bolus administration. Other studies using prolonged infusions or loading dose/maintenance infusions thus provide a better reflection of the steady state concentration–effect relations for fentanyl,[33] and these report clinically significant respiratory depression in both patients undergoing surgery[1,34,43] and volunteers[33] at a steady state C_p of 2 ng/ml or more. For this review, we define clinically significant respiratory depression as a requirement for intervention with naloxone administration, resuscitation, or cessation of fentanyl treatment.

Fentanyl-induced respiratory depression has been measured primarily by assessing the ventilatory response to carbon dioxide using the carbon dioxide rebreathing technique. Although an altered carbon dioxide response may indicate depression of central respiratory control, this approach may be impractical in patients after operation because it relies on patient cooperation and is significantly affected by alertness and arousal, conditions that are likely to vary among patients.[44] Continuous measurement of ventilation therefore is preferable, particularly to detect the occurrence of apnea, hypopnea, slow respiratory rate, or hypoxemia, the development of which will not be detected by discrete measurement.[44]

Respiratory inductive plethysmography and pulse oximetry have been used to monitor the occurrence of episodes of apnea (tidal volume < 100 ml for > 15 s in adults) and slow respiratory rate (< 8 breaths/min for > 5 min).[45–47] Using these methods, Sandler *et al.*[18] reported a baseline occurrence of three apnea episodes per hour before operation in patients undergoing thoracotomy. In the postoperative period, a steady state C_p of 1 or 2 ng/ml was associated with VAS pain scores of 2 at rest, a moderate increase in apneic episodes and slow respiratory rates, and the partial pressure of carbon dioxide arterial blood levels of 47–49 mmHg. This degree of respiratory depression did not require intervention.

There is a direct concentration–effect relation between the C_p fentanyl and respiratory depression. Plasma concentrations greater than 2 ng/ml are associated with clinically significant respiratory depression. However, the degree of respiratory depression is affected by various factors, including the types of surgical population, level of noxious stimulation, age, and individual pharmacodynamic responses. Thus, a threshold greater than 2 ng/ml should serve primarily as a guideline for clinicians.

Therapeutic Window. The therapeutic window for fentanyl analgesia is the range between the minimally effective analgesic concentration and that associated with respiratory depression.[48] Studies in volunteers al-

‡ Howell ST, Minto CF, Schlugman D, Glass PSA: Respiratory pharmacodynamics of bolus fentanyl in healthy volunteers (Abstract). ANESTHESIOLOGY 1996; 85:A339.

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Table 2. Continuous Fixed or Variable iv Fentanyl Infusion Studies (Non-PCA)

Study	Dosage	Analgesia	Mean Plasma Concentration (ng/ml)
Nimmo[14]	0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$	50% patients good	0.56–0.61
	1.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$	90% patients good	1.62–1.79
Duthie[35]	1.48 $\mu g \cdot kg^{-1} \cdot h^{-1}$	No pain 85 –93%	1.4–2.2
Duthie[49]	1.56 $\mu g \cdot kg^{-1} \cdot h^{-1}$	N/A	0.5–2.3
Holley[50]	25 $\mu g/h$	VAS 0–3	0.51–0.53
	50 $\mu g/h$		0.87–0.94
	100 $\mu g/h$		1.37–1.42
	125 $\mu g/h$		1.90–1.97
Ellis[38]	0.75–2.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (mean = 1.88)	VAS 1.4–2.0	1.16–1.19
Loper[39]	100 $\mu g/h$	VAS 1–3 (rest) VAS 4–7 (movement)	1.75
Salomaki[17]	1.67–2.41 $\mu g \cdot kg^{-1} \cdot h^{-1}$	VAS 1–2	1.38–1.54
Sandler[18]	1.4–1.6 $\mu g \cdot kg^{-1} \cdot h^{-1}$	VAS 1–3	1.5–1.7
Guinard[52]	1.25–2.0 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (mean=1.2)	VAS <3 (rest) VAS 4–7 (cough)	N/A
Bernard[51]	1.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$	VAS 1–3	1.3–1.5 (1.10)

VAS = 0–10 cm visual analog pain scale (0 = no pain, 10 = maximum pain); N/A = not applicable.

low the complex relations among analgesic effect, side effects, and fentanyl C_P to be evaluated under highly controlled conditions. In volunteers,[33] as in patients, the magnitude of analgesia and respiratory depression has a direct relation to the fentanyl C_P. The lowest concentration producing slight, but measurable analgesia, without having significant ventilatory effect in volunteers[33] and patients[14] is 0.6 ng/ml. At plasma concentrations at which pain intensity decreases by 50% (C_P associated with 50% reduction in pain intensity = 1.4 ng/ml), fentanyl decreases the slope of the V_E *versus* end-tidal carbon dioxide concentration curve in volunteers by 33% and V_E by 12%. At a C_P of 3 ng/ml, fentanyl produces profound analgesia and decreases this slope by 54% and V_E by 23%. Thus, the therapeutic margin in volunteers correlates reasonably well with that just described for patients after operation.

There is a direct concentration-effect relation between fentanyl C_P and analgesia and respiratory depression. In volunteers and patients, the range of fentanyl C_P providing analgesia without clinically significant respiratory depression is 0.6–2 ng/ml. Factors including type of surgical procedure, surgical population (*e.g.*, elderly patients), interaction with other central depressive drugs, and individual pharmacodynamic and pharmacokinetic differences can markedly influence this window and should be considered when the suggested therapeutic range is applied.

Modes of Administration. Fentanyl can be administered intravenously for postoperative analgesia using a loading (bolus) dose with a continuous fixed or variable infusion, a fixed background infusion with PCA, or PCA alone.

Continuous Background Intravenous Fentanyl Infusion. Continuous intravenous infusions of fentanyl have been used to provide postoperative analgesia after abdominal,[14,35,49] peripheral orthopedic,[35,39,50] and major spinal surgery[51]; thoracotomy[17,18,50,52]; and cesarean section delivery[38] (table 2).

Dose Requirements. An intravenous bolus of fentanyl (1 or 2 $\mu g/kg$) usually is administered before the start of infusion. If variable, the infusion rate is 1 or 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (table 2) and may be adjusted upward or downward as required by fluctuations in analgesic requirements or increasing side effects. Before the infusion rate is increased, small bolus doses of fentanyl are administered to increase the C_P rapidly.[17,18,38,39] If the infusion rate is fixed, a supplementary analgesic technique, either bolus or PCA doses of nonsteroidal antiinflammatory drugs, fentanyl, or morphine (table 2), is used to meet the therapeutic demand.[35,50,51]

Analgesic Efficacy. Infusion of fentanyl, especially at rates of 1.5–2.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$, can provide good-to-excellent postoperative analgesia (table 2). At rest, the quality of analgesia remains stable; with movement (ambulation, coughing), it decreases significantly, even with higher infusion rates.[39,52] The fentanyl C_P relates directly to the infusion rate,[50] with good analgesia at rest associated with concentrations ranging from 0.5–2.3 ng/ml.

Side Effects. Nonrespiratory side effects can occur. The incidence of nausea and vomiting after fentanyl infusion varies from 20–60%. Pruritus occurs in 0–30%

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of patients, and urinary retention occurs in 40–45%. The latter values may over- or underestimate the actual incidence of urinary retention, because many studies use postoperative indwelling urinary catheters that preclude measurement of urinary retention.

Respiratory depression is common after fentanyl infusion, but most events are not significant. Only three studies[17,50,51] have reported clinically significant respiratory depression. Comparing these three with other studies (table 2) reveals similar infusion doses, types of surgery, and other factors (*e.g.*, systemic morphine supplementation), making it unclear why the incidence of respiratory depression differed significantly. The methods of detection and measurement of respiratory depression include intermittent or continuous measurement of respiratory rate, pulse oximetry, respiratory inductive plethysmography, and intermittent arterial blood sampling.

Continuous intravenous fentanyl infusion provides good-to-excellent analgesia (particularly at rest) at doses of 1 or 2 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Naturally occurring variations in postoperative analgesic requirements can be managed by adjusting the fentanyl infusion rate upward or downward, as needed, assuming a variable infusion technique, or by parenteral administration of bolus doses of opioid or nonsteroidal antiinflammatory drugs to supplement a fixed infusion.

Continuous Background Intravenous Infusion with Patient-Controlled Analgesia. A background low-dose intravenous infusion of fentanyl may be combined with PCA to provide satisfactory analgesia with potentially fewer adverse effects.[15,36,53–58]

Dose Requirements. Patient-controlled analgesia bolus doses typically range from 7–50 μg. Background infusion rates may be fixed, ranging from 4–60 $\mu g/h$, or be variable, adjusted up and down according to clinical criteria[54,55] (table 3). Generally, the larger the background infusion rate, the smaller the PCA bolus dose. Lockout intervals (minimum time period between doses) range from "on demand" (*i.e.*, no lockout) to 15 min, the most common interval being 1–5 min (table 3).

No study directly compares the use of intravenous fentanyl infusion with and without fentanyl PCA. However, examination of the data in tables 2 and 3 reveals a smaller dose requirement for continuous infusion plus PCA than for infusion alone, despite variability in infusion rate, PCA dose, and lockout interval. The type of surgery also influences the dose requirement; that is, thoracotomy generates higher requirements than does orthopedic or lower abdominal surgery.[59]

Table 3. Patient-controlled Analgesia + Background iv Fentanyl Infusion Studies

Study	Dosage				Mean Hourly Dose	Analgesia	Plasma Concentration (ng/ml)
	Demand Bolus (μg)	Basal Infusion ($\mu g/h$)	Lockout Interval (min)	Max ($\mu g/h$)			
White[53]	10–15	30	2	150	44	VAS 2.0 (0.4–4.4)	N/A
Kay[56]	12.5	15	1–5	250	53	Pain relief rating good	N/A
Rosenberg[54]	7–13.5	32–59	None	225–315	58	VAS 2–4	N/A
Hackl[36]	9	54	1	270	88	VAS 2–3	1.54 ± 0.35 (MEC) Range 0.4–3.4
Gourlay[37]	20	20	5	180	56	Not measured	0.63 ± 0.25 (MEC) Range 0.2–1.2
Lehmann[15]	34.5	4	1	250	40–70 (0.46 $\mu g \cdot kg^{-1} \cdot h^{-1}$)	1.07 (pain scale 1–6)	1.35 ± 0.86 (MEC) Range 0.2–8.0
Welchew and Breen[57]	20	20	2	N/A	98	VAS 1–4	N/A
Lehmann[58]	34	4	1	250	40–60 (0.65 $\mu g \cdot kg^{-1} \cdot h^{-1}$)	0.3–0.6 (pain scale 1–3)	N/A
Grant[55]	50	0.75–2 $\mu g \cdot kg^{-1} \cdot h^{-1}$	15	N/A	128	VAS 1.5–5 (rest) VAS 5–7 (cough)	N/A

MEC = minimum effective analgesic concentration; Max = maximum dose allowable per hour; VAS = verbal or visual analogue score for pain (0 = no pain; 10 = worst imaginable pain); N/A = not available.

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Table 4. Patient-controlled analgesia (PCA) Fentanyl Studies without Background Infusion (PCA Only Mode)

Study*	Dosage			Mean Hourly Dose (μ/h)	Analgesia VAS Score	Plasma Concentration (ng/ml)
	Bolus (μg)	Lockout Interval (min)	Max (μg/h)			
Welchew[64]	N/A	None	600	83	2–4	N/A
Suttmann[66]	50	5	150	46.8		N/A
Rowbotham[16]	20	6	200	Not measured	2–4	1.4–1.2
Lehmann[63]	34	5	400	68 ($0.93\ \mu g \cdot kg^{-1} \cdot h^{-1}$)	2–3	N/A
Glass[19]	20	6	200	48 (0–6 h postop)	2–4 (0–6 postop)	0.3–0.4 (0–6 postop)
Laitinen[65]	50	5	500	68	1–3	N/A
Cooper[63]	20	10	120	40	2–5 (rest) 3–6.5 (cough)	N/A
Howell[60]	25	10	150	78	1–4	N/A
Ginsberg[61]	13.8–14.4	5–8	—	N/A	3–5	N/A

N/A = not available; B = demand bolus; LO = lockout interval; Max = maximum allowable hourly dose; VAS = visual analogue scale (0 = no pain; 10 = worst imaginable pain)

* Studies with VAS measurement only.

Analgesic Efficacy. The technique of background infusion plus PCA produces excellent postoperative pain relief for abdominal,[15,37,54,56,57] orthopedic[15] and peripheral vascular surgery[54] and for thoracotomy.[55,58] Consistent with the primary fentanyl infusion studies, pain has been measured in patients at rest[15,58] and increased markedly with movement.[55]

Studies of the concentration-effect relation with this technique have shown a MEC value for fentanyl for abdominal and orthopedic surgery that varies from 0.63–1.54 ng/ml.[15,36,37]

Side Effects. Nonrespiratory side effects can occur, but data regarding the incidence of adverse effects with this technique are limited. Nausea and vomiting are estimated to occur in approximately 30–40% of patients. Only two studies have investigated the incidence of pruritus, reporting a range of 7–13%,[55,58] and none have studied the occurrence of urinary retention.

Of nine studies, only five report the incidence of respiratory depression, and none show evidence of clinically significant respiratory depression requiring treatment.

Compared with continuous infusion alone, the use of a background fentanyl infusion with PCA fentanyl provides excellent postoperative analgesia, with a lower total dose consumption. The incidence of side effects with the two techniques is difficult to compare because of the limited data published for background infusion.

Patient-Controlled Analgesia. Fentanyl is rarely used alone for PCA, most likely because of the widespread belief in its brief duration of action. The opioids most commonly administered are morphine and meperidine. Consequently, only a few studies have compared the efficacy and safety of PCA fentanyl with those of other opioids,[60–62] but other investigators have used PCA fentanyl only as a control in clinical trials comparing it with other analgesic techniques[16,19,63–67] (table 4).

Dose Requirements. Consistent with other opioids used for PCA,[60,62] fentanyl dose requirements vary widely.[36,68] Bolus doses range from 20–50 μg with lockout intervals from "on demand" to 10 min. Theoretically, the lockout interval should relate to the time from drug administered to peak effect so that patients can experience the full effect of a dose before receiving a subsequent dose.[61] Because of fentanyl's short latency to peak effect,[68] a lockout interval of 5 or 6 min is reasonable.

Maximum hourly PCA dosage varies from 120–600 μg/h, and mean hourly requirements vary from 48–83 μg/h (table 4), less than those for the continuous infusion technique (table 2). Despite fentanyl's brief duration of action, patients typically require only one to three doses/h and rarely administer more than two bolus doses/h.[63,69,70] At bolus doses of 20–50 μg, fentanyl therefore might be suitable for PCA use.

Analgesic Efficacy. Good analgesia can be achieved with PCA fentanyl alone, with efficacy comparable to that of morphine and meperidine.[61,62] Only two studies,[60,67] both using small bolus doses (20–25 μg) and a long lockout interval (10 min), report inadequate analgesia.

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No study has directly compared the influence of a background infusion on the efficacy of intravenous fentanyl delivered by PCA. Comparing individual studies in tables 3 and 4 suggests that PCA fentanyl alone produces similarly effective analgesia with similar dose requirements as PCA with a background infusion. Most studies of other opioids fail to show any benefit to adding a background infusion to PCA.[71-74] Furthermore, the use of such an infusion increases opioid requirements[71-73,75] and is associated with an increased risk for severe respiratory depression.[76-78] Therefore, it may be prudent to avoid using background infusions with PCA fentanyl.

Depending on the dose and lockout interval set for the PCA device, relatively effective analgesic fentanyl C_P can be achieved and maintained with PCA fentanyl alone. In an unblinded trial of 11 patients undergoing upper abdominal surgery,[16] a bolus dose of 20 μg with a lockout interval of 6 min resulted in a mean fentanyl C_P of 1.4 ± 0.7 ng/ml (mean ± SD) 12 h after operation, which decreased to 0.5 ± 0.2 ng/ml at 48 h. Mean VAS pain scores at rest at 12 and 48 h were acceptable at 4 and 3, respectively. Comparing PCA fentanyl administered through the epidural route with PCA intravenous fentanyl in patients undergoing lower limb orthopedic or abdominal surgery, Glass *et al.*[19] conducted a randomized, double-blind, crossover trial using the same 20-μg bolus dose and 6-min lockout interval. Fentanyl C_P for the first 6 h in the intravenous PCA group ranged from 0.2–0.4 ng/ml, resulting in mean VAS scores for this period of 2 to 4 at rest (*i.e.*, moderate-to-good analgesia).

Side Effects. Only a few studies have reported the incidence of nonrespiratory side effects with PCA fentanyl alone. Nausea and vomiting occur in 20–60% of patients and pruritus occurs in 0–40%.

There are no reports of clinically significant respiratory depression with PCA fentanyl alone. However, all these studies thus far monitored respiratory depression solely by respiratory rate, which correlates poorly with ventilatory insufficiency.[44]

Patient-controlled analgesia fentanyl provides analgesia comparable to that of other intravenous modes of administration. Despite fentanyl's short duration of action, most patients require only one to three bolus doses/h. The addition of a background infusion offers no benefit to the quality of analgesia and potentially increases the risk of respiratory depression. Compared with continuous infusion, average dose consumption is less with PCA alone.

Systemic Administration: Transdermal

Transdermal delivery of fentanyl has been investigated extensively. This modality is simple, noninvasive, and allows continuous release of fentanyl into the systemic circulation. The major barrier to the entry of transdermally administered drug into the systemic circulation is the stratum corneum of the epidermis.[79] This layer of skin has a "brick-and-mortar" arrangement of keratin-rich cells embedded in a lipid matrix arranged in broad sheets forming multiple layers. However, fentanyl's lipid-soluble properties allow it to diffuse through the stratum corneum *via* the intercellular lipid medium.[80]

Passive (Conventional) Transdermal Fentanyl Administration

Permeability of the stratum corneum may be affected by various factors, including body site, skin temperature, skin damage, ethnic group, or age. To ensure a predictable rate of drug transfer, the transdermal delivery system minimizes the influence of skin in transfer by incorporating a rate-controlling membrane more impermeable than skin.

The Therapeutic Transdermal System (TTS; ALZA Corp., Palo Alto, CA) uses the membrane permeation model.[81] This transdermal fentanyl patch is available in four sizes and provides sustained release of fentanyl at rates of approximately 25, 50, 75, and 100 μg/h for periods of 48–72 h. The patch is attached to the skin by a contact adhesive, adjacent to which is a microporous membrane that controls the rate at which fentanyl is transferred from the drug reservoir to the skin (fig. 3). The reservoir is a shallow compartment with a gel matrix containing as much as 10 mg fentanyl, intended to provide a sufficiently high concentration gradient for diffusion across the skin. To prevent escape of the fentanyl matrix into the environment, the reservoir has a backing.

An important feature of the TTS design is that it takes advantage of the substantial capacity of the skin layers to act as a secondary reservoir. The presence of skin depot has several implications: It dampens the fluctuations of fentanyl effect, needs to be reasonably filled before significant vascular absorption occurs, and contributes to a prolonged residual fentanyl C^p after patch removal.[45] The amount of fentanyl remaining within the system and skin depot after removal of the patch is substantial: At the end of a 24-h period with a TTS fentanyl patch releasing drug at the rate of 100 μg/h, 1.07 ± 0.43 mg fentanyl (approximately 30% of the total delivered dose from the patch) remains in the skin depot.[24]

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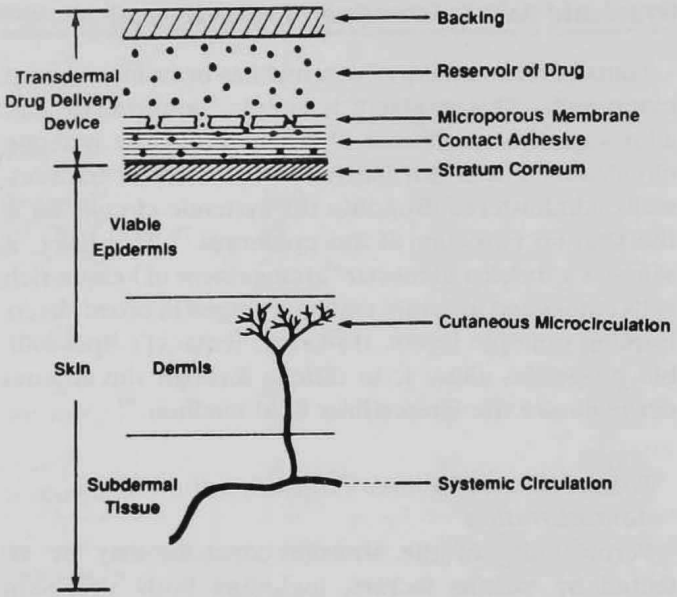

Fig. 3. The TTS-100 transdermal fentanyl delivery system. Reprinted with permission.[24]

Pharmacokinetics. Pharmacokinetic studies have examined absorption, plateau systemic concentrations, time to peak concentration, and apparent elimination half-life after removal of the TTS fentanyl patch.[24,45,49,50,82-89] There are two distinct phases of fentanyl absorption after a 24-h application of the TTS patch: An initial phase with rapid skin absorption of the drug from the contact adhesive because of the large concentration gradient between the patch and the skin reservoir, and a plateau phase with sustained release of drug from the reservoir.[24] Because of the presence of the skin reservoir, C_p peaks an average of 24 h (range, 14–28 h) after the patch is applied. During a steady state infusion, the plateau systemic concentration is proportional to the "infusion rate" of the TTS fentanyl patch (C_p = infusion rate/clearance). The plateau systemic concentration values for the TTS patch doses of 50, 75, and 100 μg/h are approximately 1, 1.5, and 2 ng/ml, respectively, well within the analgesic range for fentanyl. However, there is large interpatient variability in peak systemic concentration: Peak fentanyl C_p within 24 h of application of the 75-μg/h TTS fentanyl patch ranges from 1–5.5 ng/ml.[24,82,83,90] The actual infusion rate for the 75-μg/h patch, estimated from the formula (initial fentanyl amount − residual fentanyl amount)/duration of system application, ranges from 60–130 μg/h.[90]

When a TTS fentanyl patch is kept *in situ* for 72 h, fentanyl C_p tends to decrease after 48 h.[45,88,89] After the patch is removed, fentanyl C_p decreases slowly because of continued absorption from the fentanyl skin depot. The apparent terminal half-time ranges from 16–25 h. Mean bioavailability is 92 ± 33%, which is determined by calculating the total systemic absorption of fentanyl and measuring the total fentanyl administration (loss from the patch).[24]

Dose Requirements. Dose requirements using TTS fentanyl are difficult to match to individual patients or types of surgery, because the TTS fentanyl device is a constant-rate infusion system that requires a long time to reach a plateau C_p. In general, the patch size is selected empirically to match the magnitude of postoperative pain associated with the surgical procedure.[45] Severe postoperative pain after major abdominal surgery usually is managed with the TTS patch releasing a 100-μg/h dose, whereas mild to moderate pain after lower abdominal surgery warrants the patch releasing the 50-μg/h dose. Because the release of fentanyl from the TTS patch is similar to that from a fixed intravenous infusion, systemic opioids (morphine, fentanyl, piritramide) are used to supplement individual analgesic requirements as needed. Because of the slow attainment of an analgesic C_p, patches usually are applied before operation at varying time intervals, including immediately before surgery[84] and at 0.5,[85] 1,[91] 2,[45,49,50,79,83,86,92] and 8 h[58] after operation. The effect of a single patch application lasts 24–72 h.[45,87,90-92]

Analgesic Efficacy. The TTS fentanyl system provides a steady release of fentanyl to the systemic circulation without the flexibility of dose adjustment. This may result in poor matching to the rapidly changing intensity of postoperative pain. Thus, parenteral opioids are necessary to supplement analgesia and have been administered in all studies evaluating the transdermal patch to treat acute postoperative pain. With supplementation, TTS fentanyl produces significantly better postoperative analgesia than supplemental opioid alone, independent of the route of administration,[45,79,84-86,93] and TTS fentanyl significantly reduces the supplemental dose requirement.[45,58,79,84-86,91]

Side Effects. The incidence of nausea and vomiting with TTS ranges from 10–90%. In most studies, it is 50–60%. These values are comparable to those associated with intravenous modalities and the control groups with "rescue" opioid (morphine and meperidine) bolus administration.[45,91,93] Pruritus occurs in 4–39% of patients but typically does not require treatment. Urinary retention has been measured in only a few studies at a rate of 3–27%. Skin reaction (erythema) occurs in 20–60% of patients, but it is rarely severe enough to warrant

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Table 5. Transdermal Therapeutic System (TTS) Fentanyl: Respiratory Side Effect

Study	Delivery Rate (μg/h)	Respiratory Depression Parameter/Measurement	CSRD	
			Active (%)	Placebo (%)
Von Bormann[85]	75	SRR, PA_{CO_2}, Pa_{O_2}	1/20 (5)	0/20 (0)
Duthie[49]	100	SRR	2/9 (22)	0 (0)
Holley[50]	100	SRR	0/8 (0)	0/6 (0)
Plezia[83]	75	AP, SRR	1/7 (14)	—
Gourley[87]	50–125	SRR	3/13 (23)	—
Caplan[84]	75	SRR	0/22 (0)	0/20 (0)
Latasch[82]	75	SRR, Pa_{CO_2}	0/28 (0)	0/29 (0)
Rowbotham[86]	100	SRR	0/22 (0)	0/8 (0)
Gourlay[90]	25–75	SRR	0/20 (0)	0/20 (0)
Lehmann[63]	75	SRR	0/25 (0)	0/25 (0)
Severino[91]	25, 50	SRR, Sp_{O_2}	1/64 (2)	0/31 (0)
Sandler[45]	50, 75	AP, SRR, Sp_{O_2}	37/80 (46)	7/40 (18)
Broome[89]	20, 50, 75	SRR, Sp_{O_2}	1/61 (2)	0/20 (0)
Van Bastelaere[88]	75	SRR, Sp_{O_2}	1/20 (5)	0/20 (0)

Active = TTS group; Placebo = placebo TTS group; SRR = slow respiratory rate (<10/min); AP = apneic episodes; Sp_{O_2} = hemoglobin desaturation ≤90; TTS = transdermal therapeutic system fentanyl with rate-controlling membrane (see text); CSRD = clinically significant respiratory depression: defined as respiratory depression requiring intervention, *i.e.*, naloxone administration, resuscitation, or cessation of fentanyl treatment.

early removal of the TTS fentanyl patch and seldom persists longer than 24 h after the patch is removed.

Table 5 shows the incidence, characteristics, and severity of respiratory depression reported by TTS fentanyl studies.

Premarketing evaluation of the safety and effectiveness of the TTS fentanyl system (Duragesic; Janssen Pharmaceutica, NJ) to treat postoperative pain found a high incidence of hypoventilation, resulting, in some cases, in death.[94] A review[95] of the literature on the use of TTS fentanyl patches reveals a high incidence of clinically significant respiratory depression, confirming risk (table 5). Without further improvement in the mode of delivery or restriction of its use in closely monitored settings, the transdermal fentanyl patch delivery system cannot be recommended to treat acute pain of any origin. The Food and Drug Administration has made specific recommendations that the TTS fentanyl system should not be used to treat acute pain.

Slow onset time, inability to adjust dose during the period of application, persistent C_p, and a high incidence of respiratory depression make the transdermal fentanyl patch delivery system undesirable to treat acute pain of any origin.

Active (Iontophoretic) Transdermal Fentanyl System

To overcome the resistance to drug absorption of the stratum corneum layer of the epidermis, new methods of enhancing transdermal drug penetration and absorption are being investigated.

Iontophoresis is one method to enhance transdermal drug delivery. The system consists of a skin delivery electrode, a skin current returning electrode, and an electric power source. By applying an external electric field, electrically charged components of drug are propelled through the skin.[81] This approach for noninvasive administration has been used to deliver corticosteroids to treat joint pain,[96,97] local anesthetics (lidocaine) for analgesia for minor surgical procedures,[98] and clinically significant doses of morphine.[99]

Iontophoretic administration of fentanyl has been studied in volunteers.[100] Fentanyl (3 mg/ml) was applied for 2 h at 1 and 2 mA of current, respectively, on two occasions 2 weeks apart. Mean times to initial detection of fentanyl in the systemic circulation for the 1-mA and 2-mA applications were 33 min (range, 10–50 min) and 19 min (range, 15–20 min), respectively. Mean times to 0.5 μg/ml C_p were 92 and 36 min, and the mean times to maximum concentrations were 122 and 119 min. Maximum C_p was 0.76 ± 0.23 ng/ml (mean ± SD) with the 1-mA application and was approximately double that with the 2-mA application (fig. 4). The mean terminal half-life was similar for both the 1-mA and the 2-mA application, 354 ± 100 and 413 ± 106 min, respectively. The results indicate a significant relation between charge and the administered fentanyl dose. Fentanyl C_p increased throughout the 2-h delivery time.

Adverse events, including pruritus, transient hemoglobin desaturation, and hypoxemia occurred in several volunteers. Erythema was observed at the site of the

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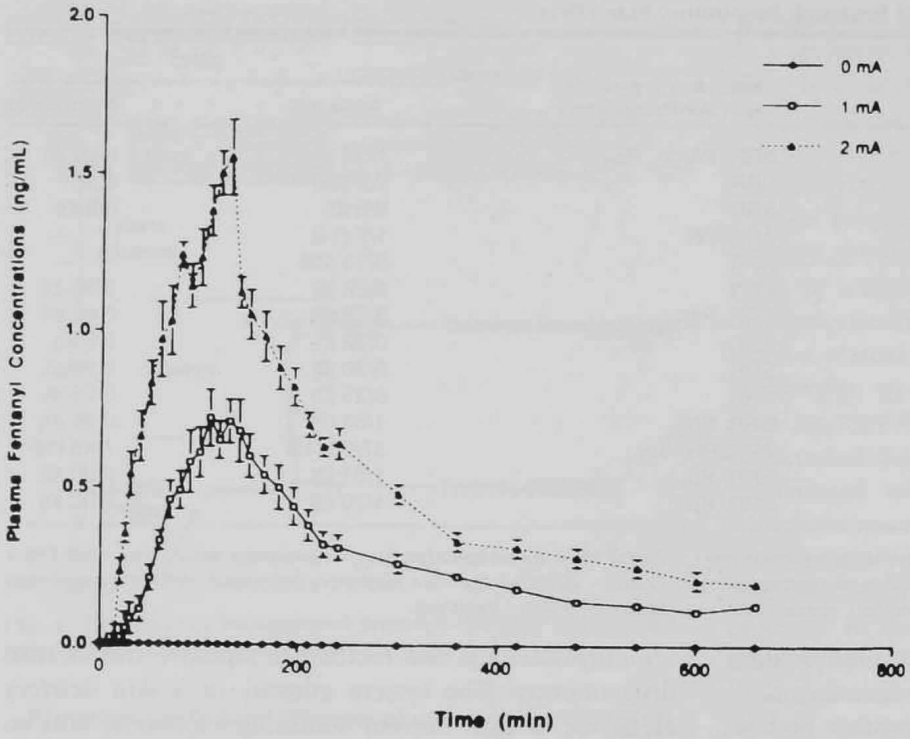

Fig. 4. Plasma fentanyl concentrations (mean ± SE) *versus* time (0–660 min) after a 120-min iontophoretic delivery at 0 mA, 1 mA, and 2 mA current. Reprinted with permission.[100]

dispersive pad but resolved without treatment within 24 h. No studies have described iontophoretic fentanyl use for postoperative analgesia.

Iontophoresis can be used to deliver clinically significant doses of fentanyl. A charge–dose relation has been documented for fentanyl administration by this method and could permit future development of noninvasive PCA using fentanyl. The terminal half-life estimated from the iontophoresis transdermal method is less than that from passive transdermal delivery of fentanyl,[24] suggesting that there may be minimal skin depot effect using iontophoresis. Further research into the pharmacokinetics and analgesic efficacy of this experimental technique is required before its introduction into clinical use.

Systemic Administration: Transmucosal

The application of opioids to mucosal surfaces to achieve an effect is not a new concept. For centuries, this route has been used to self-administer opium. In current clinical settings, fentanyl had been delivered across oral and nasal mucosal membranes to achieve effective analgesia.[101,102]

Oral Transmucosal Administration

Oral transmucosal fentanyl citrate (OTFC) incorporates fentanyl citrate in a candy mixture shaped into a lozenge on a stick. The citrate salt of fentanyl is soluble in both water and several candy matrices, and it is resistant to heat, which allows it to be incorporated into a buccal lozenge system. Oral transmucosal fentanyl citrate has been assessed thoroughly as a preoperative medication in children,[103–107] and it has produced dose-dependent increases in sedation and analgesia in adult volunteers.[108]

Pharmacokinetics. With oral transmucosal administration, fentanyl can be absorbed directly into systemic circulation through the oral mucosa or swallowed in saliva and absorbed through the gastrointestinal tract. Fentanyl absorbed through the latter route undergoes moderate first-pass extraction in the liver. Thus, the amount of saliva swallowed before adequate exposure of fentanyl to mucosal surfaces is critical in overall absorption and probably accounts for much of the interpatient variability associated with OTFC delivery.[109]

The pharmacokinetics of OTFC have been determined in volunteers.[109] Within doses ranging from 200–1,600 μg, OTFC exhibits dose-proportional pharmacokinet-

§ Streisand JB, Busch MA, Gaylord BL, Gay MA, East KA: Dose proportionality of oral transmucosal fentanyl citrate in human volunteers (Abstract). ANESTHESIOLOGY 1996; 85:A322.

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ics.§ In a study comparing oral administration of fentanyl with OTFC,[109] volunteers were given the same fentanyl dose (15 μg/kg) orally or transmucosally. The OTFC was placed in the buccal pouch and consumed in 15 min. The peak fentanyl C_p was two times greater with OTFC than with oral administration (3 ± 1 *vs.* 1.6 ± 0.6 ng/ml) and was achieved earlier (23 ± 3.4 *vs.* 101.3 ± 48.8 min).[109] Bioavailability with OTFC was 46–52%,[109],‖ compared with 32% with oral administration. Fentanyl C_p decreased to less than 1 ng/ml within 75–135 min of initial mucosal exposure to OTFC. The speed of this decrease in concentration and the comparability of terminal half-life values after intravenous and OTFC administration suggest that a fentanyl depot does not develop in the oral mucosa.[109]

Dose Requirements. Only a few studies have investigated the use of OTFC in postoperative settings.[101,110] In a double-blind, randomized controlled trial,[101] OTFC (7–10 μg/kg) was administered three times at 4-h intervals on the first postoperative day in adult patients undergoing hip or knee arthroplasty. Patient-controlled analgesia morphine supplementation was available to patients in both OTFC and control groups, as needed. The OTFC dose per treatment averaged 9.7 μg/kg. Similar VAS pain scores (VAS 2 or 3) were achieved with the two modalities, at approximately half the supplemental PCA dose in the OTFC group. Another double-blind, randomized trial[110] conducted in patients undergoing lower abdominal surgery showed that a single dose of 800 μg OTFC provided better and more sustained analgesia than a dose of 200 μg, with an onset and duration of effect similar to those achieved with a single intravenous bolus of 10 mg morphine.

Analgesic Efficacy. The median time to onset of analgesia with OTFC is approximately 4 min.[110] The duration of effect varies by patient, and doses used, ranging from 159 ± 91 min with a dose of 200 μg to 220 ± 112 min with a dose of 800 μg.[110] The quality of analgesia is good, as indicated by reported VAS pain scores of 2 or 3.[101] A single 800-μg dose of OTFC results in an onset, duration, and quality of analgesia comparable to those of a single, intravenous 10-mg bolus of morphine in patients experiencing mild to moderate postoperative pain.

‖ Dsida R, Wheeler M, Birmingham P, Henthorn T, Avram M, Klein C, Coté C: A kinetic comparison: intravenous vs oral transmucosal fentanyl in tonsillectomy patients (Abstract). ANESTHESIOLOGY 1996; 85: A1073.

Side Effects. The incidence of adverse effects with OTFC supplemented by PCA morphine appears to be comparable to that with PCA morphine alone. Pruritus, nausea, and vomiting have been reported in 20%, 40%, and 13% of patients, respectively, using OTFC plus PCA morphine and 8%, 46%, and 15% with PCA morphine alone.[101] Similarly, episodes of hemoglobin oxygen desaturation to less than 90% with OTFC and PCA morphine alone are 13% and 31%, respectively (*P* value not significant).

Oral transmucosal fentanyl citrate appears to provide analgesia of rapid onset and medium duration, comparable to that achieved with an intravenous bolus of morphine. Despite a reduction in supplemental morphine consumption, the use of OTFC did not decrease the incidence of adverse events. With limited data on the use of OTFC in the postoperative period, its role as a useful postoperative analgesic technique is not well defined.

Intranasal Administration

The surface area of the nasal cavity in a normal adult is approximately 180 cm^2, and the entire cavity is highly vascularized, with blood flow of 40 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ of tissue.[111] Although the pharmacokinetics of fentanyl *via* the intranasal route have not been evaluated, agents that are known to be lipophilic and have a low molecular weight (*e.g.,* propranolol) produce serum concentrations similar to those achieved with intravenous administration.[112] Thus, intranasal fentanyl might exhibit similar pharmacokinetic profiles.

Dose Requirements. The only two studies to date to establish a dose requirement for intranasal fentanyl compared the effects of intranasal and intravenous fentanyl in the 60 min immediately after surgery.[102,113] Fentanyl was administered with a metered device, with each spray delivering 4.5 μg fentanyl. A dose of six sprays (27 μg fentanyl) was delivered after various procedures and repeated every 5 min until patients were free of pain or refused any further analgesic. The same dose regimen was administered intravenously to the control group. An average of 3.9 nasal doses (range, 1–9 doses) of 27 μg each resulted in excellent VAS pain scores at rest in the immediate postoperative period. The mean dose requirement of 106 ± 60 μg did not differ from that in the intravenous group (99 ± 60 μg).

Analgesic Efficacy. Data from the same studies indicate mean times to onset and peak analgesic effect with intranasal fentanyl of 16.0 ± 12.6 min and 26.3 ± 15 min (mean ± SD), respectively, which are both slower than the times achieved with intravenous administration

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Table 6. Pharmacokinetic Data of Five Sequential Doses of 4,000 μg Liposomal-encapsulated Fentanyl at 12-h Interval

	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5
T_{max} (min)	16.7 ± 6.9	12.5 ± 6.3	19.2 ± 18.8	14.2 ± 8.4	18.3 ± 12.5
C_{max} (ng/ml)	2.64 ± 0.88	2.92 ± 1.4	3.3 ± 1.45	3.48 ± 1.09	3.54 ± 1.15
C_{min} (ng/ml)	0.6 ± 0.33	1.2 ± 0.6	1.5 ± 0.86	1.39 ± 0.46	0.93 ± 0.26

T_{max} = time to reach peak plasma concentration of fentanyl; C_{max} = peak plasma concentration of fentanyl; C_{min} = minimum plasma concentration of fentanyl. Adapted with permission from Hung.[120]

(10.8 ± 9 min and 20.2 ± 12 min, respectively). In part, the slow onset time with intranasal administration may have resulted from the study design with small, incremental doses. The maximum pain-relieving effect was the same with both techniques.

Side Effects. Intranasal fentanyl did not irritate the nasal mucosa and produced only minimal respiratory effects (mild hemoglobin desaturation in 1 of 53 patients) and an incidence of nausea, vomiting, and euphoria less than 1%.

The value of intranasal administration of fentanyl for postoperative analgesia needs to be further defined. Based on only two studies, it appears that intranasal delivery of fentanyl can produce analgesia similar to that achieved by intravenous administration. However, use of a low dose slows onset time.

Systemic Administration: Transpulmonary

Transpulmonary (inhalational) administration of medication produces rapid, effective drug delivery as a result of the thin alveolar-blood barrier, high tissue perfusion, and enormous surface area of the lungs. Delivery of morphine through the pulmonary system has proved effective.[114,115] Fentanyl also can produce postoperative analgesia if administered as a nebulized aerosol.[116,117] To overcome fentanyl's short duration of action, a liposome-encapsulated drug carrier system has been developed. Liposomes are microscopic vesicles composed of an aqueous compartment surrounded by a phospholipid bilayer that acts as a permeable barrier to entrap molecules.[118] Incorporation of a drug within a liposome provides a controlled, sustained release system.

Pharmacokinetics

Data on the pharmacokinetics of transpulmonary fentanyl are limited. Inhalation of 300 μg fentanyl from the nebulizer produces a peak C_P of 0.4 ng/ml at 2 min and a plateau C_P of 0.1 ng/ml at 15 min. With inhalation of 100 μg, fentanyl C_P remains stable at a concentration close to the detection limit of 0.02 ng/ml.[116]

In a study comparing nebulizer and intravenous administration of fentanyl,[119] delivery of 2,000 μg of a nebulized mixture of free (50%) and liposomal-encapsulated (50%) fentanyl (FLEF) to volunteers resulted in a peak C_P of 1.15 ng/ml at 22 min. Although venous blood was sampled in this study, this should be of little consequence because, at 22 min, arterial and venous concentrations differ minimally. One important feature of the FLEF was that the C_P decreased slowly after the single 2,000-μg dose: At 8 and 24 h after inhalation, fentanyl C_P values were 0.25 ± 0.14 ng/ml and 0.12 ± 0.16 ng/ml, respectively.

In a subsequent study,[120] five doses of 4,000 μg FLEF were administered at 12-h intervals. The time to reach the peak concentration after each administration ranged from 12.5–19.2 min, and the fentanyl C_P was maintained within the analgesic therapeutic concentration; that is, 0.6–3 ng/ml (table 6). The bioavailability of inhaled FLEF is 12–20%,[119,120] which is consistent with the bioavailability of most drugs administered *via* the pulmonary system (10–20%).[121]

Dose Requirements. A dose of 300 μg fentanyl administered *via* an oxygen-driven nebulizer significantly decreases pain after various surgical procedures.[116] It also significantly increases the median time to the first supplemental dose of parenteral morphine relative to control (190 *vs.* 9 min, respectively). However, in another study in which a single nebulized dose of 3 ml fentanyl citrate solution of different concentrations (100, 250, and 500 μg/ml) administered progressively in 9 min, only the highest dose (500 μg/ml) resulted in a moderate analgesic response within 5 min of inhalation.[117] The differences in these results probably can be accounted for by differences in study design, nebulizer administration technique, and surgical population. No studies have reported the dose requirements for inhaled liposomal-encapsulated fentanyl in patients after operation.

Analgesic Efficacy. After inhalation of nebulized fentanyl, moderate analgesia is achieved in 5 min,[117] the time when C_P peaks.[116] However, this analgesic effect

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lasts only 2 h. The FLEF mixture has the potential to prolong the analgesia, as indicated by the presence of a therapeutic concentration 12 h after inhalation of a single dose of 4,000 μg.[119]

Side Effects. No clinically significant respiratory depression or evidence of respiratory tract irritation has been reported in the few patients studied thus far, nor is there any significant difference in nausea and drowsiness relative to controls.

Inhalation of fentanyl offers an easy, noninvasive route of administration. Onset of effect is rapid after nebulizer administration of fentanyl at a high dose (1,500 μg). However, the duration of action with this technique is too brief for routine clinical use. The liposome-encapsulated method significantly prolongs the effect of fentanyl, but it slows the onset of analgesia. Additional study is required to determine the safety and efficacy of transpulmonary fentanyl administration for postoperative analgesia.

Neuraxial Administration

Epidural and intrathecal administration of fentanyl are long-established routes for intraoperative anesthesia and postoperative analgesia. The pharmacokinetics of epidural delivery have been well-studied, but relatively little is known about the systemic kinetics of intrathecal fentanyl.

Pharmacokinetics

The main routes of distribution after administration of fentanyl into the epidural space include (1) movement across the meninges into the cerebrospinal fluid (CSF); (2) movement from the CSF into the opioid receptor or other nonspecific binding site in the spinal cord; (3) rostral migration *via* the CSF to supraspinal sites; (4) vascular absorption in the epidural or spinal vascular system; and (5) uptake into epidural fat.

Factors that affect dural penetration include lipid solubility, molecular weight, molecular shape, and the degree of molecule ionization.[122–124] Lipid solubility, as assessed by the octanol–buffer partition coefficient, correlates with the permeability coefficient in a nonlinear manner. The optimal octanol–buffer distribution coefficient that results in maximal meningeal permeability lies between 129 (alfentanil) and 560 (bupivacaine).[123] This relation between lipid solubility and the meningeal permeability coefficient of a drug can be explained by the dual nature of the arachnoid mater, which is the principal meningeal permeability barrier.[123] To cross the arachnoid mater, a drug molecule must diffuse through the hydrophilic domain (*e.g.*, extracellular and intracellular fluid) and hydrophobic domain (*e.g.*, cell membrane lipids). Lipophilic drugs readily dissolve in the lipophilic component of the arachnoid mater and thus cross the region easily. The hydrophilic zone is more difficult for these drugs to penetrate, creating the rate-limiting factor for diffusion *via* the arachnoid membrane. As a result, membrane permeability is highest in the opioids having intermediate lipid solubility (*e.g.*, fentanyl).

Because of its high octanol–buffer partition coefficient, fentanyl also has high vascular permeability and moves as easily into the intravascular compartment as into the subarachnoid compartment. The extent of vascular absorption is influenced by various factors, including dose administered, the mode of administration (bolus *vs.* infusion), and, possibly, concurrent use of epinephrine.

After epidural bolus administration, systemic absorption of fentanyl increases as the bolus dose increases. For example, administration of a bolus of 30–70 μg (~ 0.5–1 μg/kg) results in a peak fentanyl C_P less than 0.2 ng/ml in the first 30 min,[125,126] which is much less than the range for MEC. However, within 10–30 min of an epidural bolus of 100–200 μg (~ 1.5–3 g/kg), the plateau systemic concentration is 0.3–0.86 ng/ml,[41,126–128]; that is, it is within the range of the MEC.

With continuous epidural infusion of fentanyl, clearance from the blood determines the blood concentration at steady state. Continuous infusion of doses resulting in good analgesia produces significant fentanyl C_P (1 or 2 ng/ml) after several hours of administration.[18,19,38,39,129,130] Studies comparing therapeutic doses of epidural and intravenous fentanyl for postoperative pain relief show similar fentanyl C_P values at equal and equianalgesic doses (table 7A).[18,19,38,39] With thoracic epidural administration (*i.e.*, thoracotomy), dose requirements[17,131] and C_P[17] are lower compared with lumbar epidural administration, but systemic absorption remains significant.[17] There are no published data on the pharmacokinetics of fentanyl in CSF with continuous epidural infusion or repeated bolus administration (patient-controlled epidural analgesia [PCEA]).

Adding 1:300,000 epinephrine to a continuous thoracic epidural infusion of fentanyl significantly reduces the fentanyl C_P and, relative to intravenous delivery, the equianalgesic dose.[132] This effect may be caused by a

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Table 7. Prospective, Randomized Clinical Studies Comparing the Use of Fentanyl *via* Different Routes

Study	Site of Epidural	Surgery	Analgesia	Plasma Concentration	Respiratory Side Effects*	Other Side Effects	Dose Requirement
Epidural *vs.* intravenous							
Ellis[38]	L	C-section	NSD	NSD (24 h)	NSD	NSD	NSD
Loper[39]	L	Knee	NSD	NSD	NSD	NSD	NSD
Glass[19]	L	Lower abdomen/ extremity	NSD	NSD	NSD	NSD	NSD
Cooper[67]	L	C-section	EP>IV	N/A	NSD	NSD	NSD
Grant[55]	L	Thoracotomy	NSD	N/A	NSD	NSD	28% ↓ inEp
Sandler[18]	L	Thoracotomy	NSD	NSD	NSD	NSD	25% ↑ inEp
Guinard[52]	L	Thoracotomy	NSD	N/A	NSD	Pr-NSD N (IV >Ep)	NSD
Baxter[150]	L	Thoracotomy	NSD	NSD	NSD	NSD	NSD
Salomaki[17]	T	Thoracotomy	NSD	EP <IV	IV>EP	NSD except N,S(IV>Ep)	43% ↓ inEp
Welchew[57]	T	Upper abdominal	NSD	N/A	N/A	NSD	55% ↓ inEp
Guinard[52]	T	Thoracotomy	NSD	N/A	NSD	Pr-NSD N (IV >Ep)	NSD
Thoracic *vs.* lumbar epidural							
Coe[149]	—	Thoracotomy	NSD	N/A	NSD	NSD	NSD
Guinard[52]	—	Thoracotomy	NSD	N/A	NSD	NSD	NSD
Sawchuck[131]	—	Thoracotomy	NSD	N/A	L >Th	NSD	NSD
Bouchard[160]	—	Thoracotomy	NSD	NSD	NSD	NSD	NSD

NSD = no significant difference throughout the whole study period; N/A = not available; L = lumbar epidural; Th = thoracic epidural; Pr = pruritus; N = nausea and vomiting; S = sedation; Ep = epidural group; IV = intravenous group; Dose requirement = either presented as cumulative dose or average infusion rate.

* Clinically significant respiratory depression: defined as respiratory depression requiring intervention *i.e.,* naloxone administration, resuscitation, or cessation of fentanyl treatment.

reduction in vascular uptake resulting from vasoconstriction or by a direct α-agonist activity of epinephrine.[133]

Once in the CSF, fentanyl, similar to other opioids, spreads rostrally. The CSF concentration at the level of the cervical spine peaks within 20 min,[125] compared with 3 h for morphine[134] and 1 h for meperidine.[135] Because of the high affinity of fentanyl with nonspecific binding sites in the lipid-rich spinal cord,[136] only a small proportion (~10%) of the administered dose migrates to the cervical region.[125]

Fentanyl also can migrate from the CSF into the epidural vascular compartment *via* the dura. However, little is known about the systemic pharmacokinetics of intrathecal fentanyl. At an average intrathecal infusion rate of 0.8 $mg \cdot kg^{-1} \cdot h^{-1}$ after thoracotomy, vascular absorption is significant and fentanyl C_P values range from 0.49–0.72 ng/ml.[137] However, this range reflects C_P values much lower than plasma analgesic concentrations when intravenous fentanyl infusion is used for post-thoracotomy analgesia (1.4–1.6 ng/ml).[17,18] This difference suggests that analgesic effect is mediated in part at the spinal level.

Epidural Administration

More than 40 published clinical trials document epidural fentanyl administration and effect. Most suggest that epidural fentanyl is less likely than morphine to produce clinically significant ventilatory depression.[138] However, respiratory arrest has been reported.[139] Fentanyl is reported to be associated with fewer minor adverse effects (nausea, vomiting, pruritus, sedation, urinary retention).[140,141] The modes of epidural administration are the same as those used intravenously, *i.e.,* bolus dose alone, bolus dose combined with continuous infusion, continuous infusion alone, PCEA, and PCEA with a continuous fixed or variable background infusion. Both trauma and postsurgical populations have been studied, including patients with fractured ribs,[142] those recovering from abdominal[19,127,143–147] and orthopedic surgery,[39,129] cesarean section,[38,148] thoracoto-

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my,[17,18,52,130,131,149–153] and radical prostatectomy.[154] In addition, epidural fentanyl often is combined with local anesthetic agents (particularly bupivacaine) and other adjuvant drugs (epinephrine, clonidine, other opioids) to provide postoperative analgesia, pain control for labor and delivery, and relief from perioperative cesarean section pain. These combined techniques are not discussed in this review.

Dose Requirements. The dosage of fentanyl used for repeated single bolus administration varies from 50 to 200 μg (approximately 1–3 μg/kg,[127,143,155,156]) and up to 5 μg/kg.[157] Analgesia begins within 15 min and lasts 2 to 4 h.[126,127,143,155,157] Increasing the diluent volume to 10–25 ml[155] and using a concentration of 10 μg/ml[158] speeds onset time and increases the duration of action. However, the duration of analgesia provided by a bolus dose of fentanyl is brief, making administration by infusion necessary for adequate postoperative pain relief.

Epidural infusion rates range from 0.5–2.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Epidural or intravenous bolus opioid (usually fentanyl) supplementation may be used to achieve or maintain good analgesia, especially if the infusion rate is fixed.[52,144] In addition, PCEA has been used after operation, often with a background infusion, but in some cases alone.[19,67,147,159–161] Doses of 20–25 μg with a lockout interval of 6–10 min and background infusion rates of 0.5–1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ are most common. Variability in dose requirements, particularly in the first 24 h after operation, may be associated with differences in anesthetic technique (*e.g.*, epidural *vs.* general anesthesia), intraoperative opioid administration, the magnitude of postoperative pain after different surgical procedures, or all of these.[162]

Analgesic Efficacy. Continuous epidural fentanyl infusion, PCEA, or both provide excellent analgesia and overcome the limitations to the duration of action associated with epidural bolus administration. Although analgesia is excellent at rest, pain scores increase with movement and coughing.[39,52,127,152,154,157] This is in contrast to the good analgesia at rest and with ambulation or coughing provided by intrathecal administration of fentanyl.[137,163]

Several investigators have compared the efficacy of intravenous and epidural fentanyl in a series of controlled trials conducted in different postoperative patient populations.[18,19,38,39,52,55,57,67,150] Whether the two techniques provide equivalently effective analgesia is controversial. To put the argument in perspective, several parameters are required for comparison: analgesic effect, dose requirement, C_p, and respiratory and nonrespiratory side effects. Equally important are the site and type of surgery and the site of epidural catheterization (*i.e.*, lower abdominal or orthopedic surgery using a lumbar epidural catheter,[19,38,39,67] upper abdominal surgery or thoracotomy using a lumbar epidural catheter,[18,52,53,150] or upper abdominal surgery or thoracotomy using a thoracic epidural catheter [table 7A]).[17,52,57]

Intravenous and epidural fentanyl provide equivalent analgesia in these surgical populations. Dose requirements are similar with the two modes of administration (*e.g.*, a bolus plus infusion or PCEA). However, some investigators report that placing the catheter at a dermatomal level corresponding to the surgical site (thoracic placement for thoracotomy[17] and upper abdominal surgery[57]) decreases the hourly and cumulative dose requirement for epidural delivery by 50% compared with intravenous. In contrast, other investigators report no significant differences in the analgesic dose requirements associated with thoracic *versus* lumbar epidural catheters for upper abdominal or thoracic surgery (table 7B).[52,131,149,160] Similarly, neither the fentanyl C_p associated with analgesia nor the side effect profiles for the two techniques differ significantly. Overall, these findings indicate little clinical advantage to providing postoperative analgesia by the epidural rather than intravenous route of administration.

Side Effects. Most reviews of the nonrespiratory side effects of intrathecal and epidural opioids focus on morphine.[164–166] With epidural fentanyl, the most common side effect is pruritus, with an incidence of 0–85%. It usually appears within an hour after bolus epidural injection and lasts 20–30 min. Fentanyl-induced pruritus does not appear to be related to histamine release and can be antagonized with naloxone.[164] Features that distinguish epidural fentanyl-induced pruritus from that resulting from epidural morphine include diminished intensity[140] and localized (segmental or regional) effect. The facial area rarely is involved.[141,167] Cutaneous flare and urticaria are uncommon.[140,141] Treatment is rarely necessary.

The incidence of nausea and vomiting with epidural fentanyl is approximately 20–30%, which is comparable to other epidural opioids.[166] Nausea usually occurs within 3 h of fentanyl administration.[140] Treatment with antihistaminic agents, opioid agonist or antagonists, or pure opioid antagonists is common.[160,168]

Epidural opioids can produce dose-independent, naloxone-reversible urinary retention. The mechanism of this effect is believed to be secondary to the interaction of epidural opioids with opioid receptors in the sacral

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Table 8. Epidural Fentanyl Studies: Respiratory Side Effects

Study	Dosage	Respiratory Depression Parameter/Measurement	CSRD	%
Carrie[191]	B-150-200 μg	SRR	No	0
Lomesey[127]	B-200 μg	SRR, Pa_{CO_2}	No	0
Robertson[167]	B-100 μg×2	SRR	No	0
Ahuja[179]	B-1.5 μg/kg; I-0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$	SRR, Pa_{CO_2}	No	0
Negre[41]	B-200 μg	SRR, VE, ET_{CO_2}	No	0
Renaud[129]	B-1 μg/kg; I-1 $\mu g \cdot kg^{-1} \cdot h^{-1}$	SRR, VE, ET_{CO_2}	No	0
Chrubasik[146]	B-100 μg; I-200 μg/h	SRR, Pa_{CO_2}	No	0
Gough[128]	B-1.5 μg/kg; I-0.6 $\mu g \cdot kg^{-1} \cdot h^{-1}$	SRR	No	0
Kreitzer[192]	B-100 μg, I-1.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$	SRR	No	0
Melendez[151]	B-200 μg (repeated)	SRR,Pa_{CO_2}	No	0
Badner[130]	B-1.5 μg/kg; I-1.47 $\mu g \cdot kg^{-1} \cdot h^{-1}$	SRR,AP,Pa_{CO_2}	No	0
Ellis[38]	B-1.5 μg/kg; I-1.52 $\mu g \cdot kg^{-1} \cdot h^{-1}$	SRR, ET_{CO_2}	No	0
Loper[39]	I-100 μg/h	SRR	No	
Salomaki[17]	B-variable; I-0.95 $\mu g \cdot kg^{-1} \cdot h^{-1}$	SRR,Pa_{CO_2},AP	No	0
Coe[149]	B-1.5 μg/kg; I-0.57–0.69 $\mu g \cdot kg^{-1} \cdot h^{-1}$	SRR	No	0
Grant[55]	PCEA:B-50 μg; I-0.75–2 $\mu g \cdot kg^{-1} \cdot h^{-1}$	SRR,Pa_{CO_2}	No	0
White[140]	B-40-100 μg; I-20–80 μg/h	SRR,Pa_{CO_2}	No	0
Guinard[52]	I-1.15–1.22 $\mu g \cdot kg^{-1} \cdot h^{-1}$	SRR,AP,SP_{O_2},Pa_{CO_2}	No	0
Sandler[18]	B-0.5–1.5 μg/kg; I-1.95 $\mu g \cdot kg^{-1} \cdot h^{-1}$	SRR,AP,Pa_{CO_2}	No	0
Sawchuck[131]	B-25–50 μg; I-1.55–2.06 $\mu g \cdot kg^{-1} \cdot h^{-1}$	SRR,Pa_{CO_2}	4/30	13%
Owen[147]	(1)PCEA:B-25 μg, LO-15 min (2)PCEA as 1 plus I-50 μg/h (3) I-50 μg/h ± B-25 μg	Sp_{O_2}<94%, Sp_{O_2}<85%	No	0
Benzon[152]	I-60–63 $\mu g \cdot kg^{-1} \cdot h^{-1}$	SRR,Pa_{CO_2},Sp_{O_2}	No	0
Geller[144]	B-60 μg; I-20 μg/h	SRR,Pa_{CO_2}	No	0
Baxter[150]	b-1.5 μg/kg; I-1μg $\cdot kg^{-1} \cdot h^{-1}$*	SRR,AP,Sp_{O_2}	7/25	28%
Salomaki[193]	I-20–100 μg/h	Pa_{CO_2},SRR	No	0
Bouchard[160]	PCEA: B-25 μg; LO-10 min	SRR	No	0
Cooper[67]	PCEA: B-20 μg; LO-10 min	SRR	No	0
Joshi[194]	B-20 μg; I-8–20 μg/h	Not specified	No	0

B = bolus; I = infusion; PCEA = patient-controlled epidural analgesia; LO = lockout interval; SRR = respiratory rate <8–10; AP = apnea episode; Sp_{O_2} = desaturation <90%, Pa_{CO_2}- ↑ Pa_{CO_2}>50 mmHg; CSRD = clinically significant respiratory depression: defined as respiratory depression requiring intervention, *i.e.* naloxone administration, resuscitation, or cessation of fentanyl treatment.

* Morphine supplementation via patient-controlled analgesia.

spinal cord.[169] This interaction inhibits sacral parasympathetic neural outflow, relaxing the bladder detrusor muscle, increasing the maximum capacity of the bladder, thereby resulting in urinary retention.[170,171] The reported incidence of urinary retention ranges from 0–50% but is less than 12% in most studies. Data on the incidence of urinary retention after epidural fentanyl are limited by the common postoperative practice of placing or maintaining an indwelling urinary catheter.

Respiratory depression (table 8) is the most serious adverse effect of the use of epidural opioids. Various factors may contribute to its occurrence with epidural fentanyl, including the use of additional opioids or sedative drugs, antiemetics, or prolonged infusions.[172,173]

Initially, the lipophilic properties of fentanyl were thought to confer minimal risk of delayed respiratory depression due to poor cephalad spread in the CSF. However, the single human CSF pharmacokinetic study of epidural fentanyl bolus administration at the lumbar level shows that maximum CSF concentrations in the cervical region are as much as 10% of CSF concentration in the lumbar region.[125]

Clinically significant respiratory depression can occur with either bolus doses or continuous infusions of epidural fentanyl. The carbon dioxide ventilatory response curve is depressed after an epidural bolus dose of 200 μg.[41] However, incidents of respiratory arrest[139,174] and profound respiratory depression[175–178] have been reported after a 100-μg dose. Epidural infusions of fentanyl ranging from 0.5–1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ depress the carbon dioxide ventilatory response curve.[129,179] Despite these data, clinically significant respiratory depression appears to be relatively rare with epidural fentanyl. Of those 29 studies with a total of approximately 600 patients that

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Table 9. Intrathecal Fentanyl Studies: Postoperative Analgesia

Study	Surgery	Mode/Bolus	Analgesia	Onset (O) (min)/Duration (D) (h)	Nausea Vomiting	Pruritus	CSRD
Jacobson[183]	Foot	Bolus 25 μg	Complete relief	O 5–10/D 4	None	None	None
Jacobson[186]	Postamputation (phantom limb pain)	Bolus 25 μg	Complete relief	O 5–10/D 8	None	Present*	None
Tobias[184]	Exploratory laparotomy	Infusion 0.2 μg · $kg^{-1} \cdot h^{-1}$	PS 0–1	—	None	None	None
Domsky[182]	Hip	PCA Bolus 6 μg LO 1–1.5 h	VAS 5 (0–12 hr) VAS 3–5 (12–2 h) VAS 1–3 (24–48 h)	O 15	None	None	None
Honet[188]	1st stage labor	Bolus 10 μg (15.5 ± 5.1 μg)†	VAS 3–4	O 20/D 1.3	Present*	Present*	N/A
Reuben[185]	Lower extremity vascular surgery	Bolus 5 μg	VAS 5–7	N/A	0/10	0/10	None
		10 μg	VAS 3–7	O 2–3/D 1	0/10	1/10	
		20 μg	VAS 1–3	O 3–5/D 2	0/10	0/10	
		40 μg	VAS 0–2	O 2–3/D 5	0/10	1/10	
		50 μg	VAS 0–2	O 2–3/D 5	1/10	5/10	
Sudarshan[166]	Thoracotomy	Bolus 50–150 μg	VAS 1–2 (rest/movement)	O 60/D 4–10	None	3/10	None

VAS = visual analogue scale (0 = no pain; 10 = worst imaginable pain); PS = Hannallah-Rice-Broadman (OPS) scale: a scoring system from 0–10;[195] LO = lockout interval; N/A = not available; CSRD = clinically significant respiratory depression defined as respiratory depression requiring intervention, *e.g.* naloxone treatment, resuscitation, or cessation of fentanyl treatment.

* Side effect occurred but severity or incidence not recorded.

† Average first dose.

evaluated the incidence and severity of respiratory side effects, the overall incidence of clinically significant depression is approximately 1.8%. All these incidences of respiratory depression occurred in two of the studies.[131,150] In one study,[131] administration of fentanyl through a thoracic or lumbar catheter at an average infusion rate of 1.55–2.06 μg · $kg^{-1} \cdot h^{-1}$ resulted in respiratory depression requiring naloxone intervention in 4 of 30 patients. In the other study,[150] it is difficult to assess the clinical significance of the respiratory depression because the protocol demanded arterial blood gas sampling every 2 h and administration of naloxone to each patient in whom the partial pressure of carbon dioxide in arterial blood exceeded 50 mmHg (7 of 25 patients), regardless of clinical status.

Epidural administration of fentanyl can provide good to excellent postoperative analgesia. Bolus administration produces a rapid onset but short duration of effect. A continuous infusion or PCEA is therefore more common in the postoperative setting and provides excellent analgesia at rest. (As with other routes of administration, the analgesic effect diminishes with movement and coughing.) Compared with intravenous administration, the analgesic efficacy, dose requirement, C_p, respiratory and nonrespiratory side effects of epidural and intravenous fentanyl are similar, indicating no advantage to using epidural rather than intravenous fentanyl infusion alone for postoperative analgesia.

Intrathecal Administration

Intrathecal fentanyl usually is combined with local anesthetic agents for perioperative anesthesia and analgesia, particularly in obstetric patients.[180,181] Only a limited number of reports, many of them single cases, document the use of intrathecal fentanyl alone for postoperative analgesia[182–184] (table 9). Modes of administration include single bolus injection,[183,185,186] intrathecal catheterization, repeated observer-administered or PCA boluses,[163,181] and continuous infusion *via* an intrathecal catheter.[137,184,187] Repetitive bolus injection of fentanyl *via* an intrathecal catheter also has been assessed as the sole source of analgesia during the first stage of labor.[188]

Dose Requirements. The minimum intrathecal bolus requirement for postoperative analgesia is 20 μg.[185] In obstetric patients, a smaller dose (10 μg) is effective

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(table 9). Onset of analgesia is usually within 5–15 min, but duration is variable, ranging from 1–5 h in most reports. Intrathecal fentanyl has also been administered as PCA *via* an intrathecal catheter. Although the ideal bolus size and lockout interval for intrathecal fentanyl *via* PCA remain unknown, good analgesia with no clinically significant adverse effects can be achieved with bolus doses of 6 μg and a lockout interval of 1–1.5 h.[182]

At an average infusion rate of 0.8 $\mu g \cdot kg^{-1} \cdot h^{-1}$, continuous intrathecal infusion produces satisfactory analgesia in patients having thoracotomy.[137] A rate of 5 μg/h (*i.e.*, approximately 0.065 $\mu g \cdot kg^{-1} \cdot h^{-1}$) in a similar surgical population resulted in inadequate postoperative analgesia and the need for parenteral opioid supplementation in nearly all patients.[187]

Analgesic Efficacy. Effective postoperative analgesia can be achieved with intrathecal bolus doses of 20 μg (table 9). Increasing this dose to 50 μg produces excellent analgesia at rest, neutralizes the effects of ambulation or coughing on the quality of analgesia in patients after thoracotomy, and improves postoperative pulmonary function compared with PCA morphine alone.[163] Similar analgesic efficacy also can be achieved with an intrathecal infusion at 0.8 $\mu g \cdot kg^{-1} \cdot h^{-1}$,[137] which also overcomes the painful effects of movement and coughing with greater speed than thoracic epidural or intravenous fentanyl at infusion rates of 1.22 and 1.27 $\mu g \cdot kg^{-1} \cdot h^{-1}$, respectively.[50] Thus, the intrathecal route provides better and more complete analgesia than fentanyl administered by other modalities that rarely provide dense analgesia with movement or coughing. A potential limitation to the use of the intrathecal technique is the need for an indwelling intrathecal catheter, which confers the risk for infection or neurotoxic effects (with local anesthetic agents), and necessitates clinical expertise in catheter placement and maintenance.

Side Effects. Side effects are relatively minor with intrathecal fentanyl, and only a few studies report any incidence of nausea or mild-to-moderate pruritus. However, these symptoms develop with both relatively large bolus doses (*e.g.*, a 50-μg bolus dose) and low-dose infusions (*e.g.*, 5 μg/h for 24 h; table 9). A 30% incidence of urinary retention has been reported at a low-dose continuous infusion of 5 μg/h progressively in 24 h.[187]

Clinically significant respiratory depression has not been reported with the use of intrathecal fentanyl (table 9), even at total doses as high as 100 μg delivered directly into the subarachnoid space.[163] In contrast, the same dose of fentanyl (100 μg) delivered epidurally has been associated with severe respiratory depression. Several explanations may account for this difference in effect. First, intrathecal administration results in lower systemic absorption than does epidural delivery.[137] Second, the intrathecal dose requirement generally is lower than the epidural requirement, which further reduces the risk of dose-related ventilatory depression. Finally, studies of intrathecal fentanyl administration involve only small numbers of patients, potentially making it difficult to detect a statistically significant incidence of respiratory depression.

Compared with epidural administration, fentanyl delivery *via* the intrathecal route provides more intense and complete analgesia at rest and with movement, at a lower dose requirement than either the epidural or intravenous routes. Vascular absorption occurs but to a lesser extent. However, the requirement of an indwelling intrathecal catheter introduces the risk for infection or neurotoxic effects, limiting the popularity of this technique for use after operation.

Conclusions

Fentanyl is used widely as an analgesic agent in the postoperative or critically ill patient. Because of its physical properties and potency, it is effective *via* multiple routes of administration; noninvasive routes are being developed. Subarachnoid use provides the most intense, complete analgesia, although intravenous PCA, with its more convenient format, also is effective. Adverse effects are apparent with all modes of administration. Pruritus, urinary retention, and nausea and vomiting are common, and all patients receiving fentanyl for postoperative analgesia require vigilant monitoring to detect and treat respiratory effects. New experimental modalities, especially iontophoretic application and transmucosal delivery, present promising opportunities for postoperative analgesia.

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