

Absorption Characteristics of Transdermally Administered Fentanyl

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Fentanyl was administered intravenously and transdermally to eight surgical patients to determine the systemic bioavailability and rate of absorption of the transdermally administered drug. Serum fentanyl concentrations reached a plateau approximately 14 h after placement of the transdermal fentanyl delivery system. This plateau was maintained until removal of the system at 24 h. The decline in serum fentanyl concentrations after removal of the transdermal system had a terminal half-life of 17.0 ± 2.3 h (mean \pm SD), considerably longer than the terminal elimination half-life seen after intravenous administration of fentanyl in the same patients (6.1 ± 2.0 h). The rate of fentanyl absorption, predicted to be $100 \mu\text{g/h}$ from *in vitro* data, appeared to be relatively constant during a period starting 4–8 h after placement of the transdermal system until removal of the system at 24 h. The rate of absorption during this period was $91.7 \pm 25.7 \mu\text{g/h}$. After removal of the transdermal fentanyl delivery system, absorption continued at a declining rate. This indicates that the long terminal half-life of serum fentanyl concentrations after transdermal system removal is due to continued slow absorption of fentanyl, probably from a cutaneous depot of drug at the site of prior transdermal system placement. At the time of removal of the transdermal fentanyl system, 1.07 ± 0.43 mg of drug remained in this depot. Systemic fentanyl bioavailability was found to be 0.92 ± 0.33 , with no evidence of significant cutaneous metabolism or degradation by the skin's bacterial flora. The transdermal administration of fentanyl produces relatively constant serum fentanyl concentrations for significant periods of time in the postsurgical patient requiring analgesic therapy. (Key words: Analgesia, postoperative. Anesthetics, fentanyl: bioavailability. Anesthetic techniques, transdermal: fentanyl. Pharmacokinetics, fentanyl.)

TRANSDERMAL DRUG ABSORPTION may offer several advantages over other routes of drug administration. The skin acts as both a barrier and a reservoir for a transdermally administered drug. This causes the drug to be absorbed slowly and released in a sustained manner, pro-

ducing relatively constant serum drug concentrations for long periods of time. These characteristics eliminate the peak and trough blood levels (with the attendant high likelihood of alternating periods of over- and under-dosing) seen with periodic intravenous, intramuscular, or oral dosing regimens.

In the last 15 yr, much work has been done to explore the potential of transdermal drug administration. Transdermal dosage forms for nitroglycerin,^{1,2} scopolamine,^{3,4} clonidine,^{2,3,5} and estradiol³ have been developed and approved for use in the USA. Transdermal administration of these drugs is convenient and, as expected, produces relatively constant serum concentrations for long periods of time.^{1,5}

Opioids can be absorbed percutaneously. A transdermal fentanyl delivery system (Transdermal Therapeutic System of fentanyl, TTS-Fentanyl 100, Alza Corporation, Palo Alto, CA) has been developed for use in the management of moderate to severe pain. Holley and van Steennis found this transdermal system to be as effective in obtaining analgesic serum fentanyl concentrations as a 24 h continuous iv infusion of fentanyl at a rate of $100 \mu\text{g/h}$.⁶

Serum fentanyl concentrations measured after placement of a transdermal fentanyl system reflect the net effects of absorption, distribution, and elimination. These effects can not be isolated from each other using only serum fentanyl measurements obtained following transdermal administration of the drug. Distribution and elimination characteristics for a patient can only be determined by an intravenous pharmacokinetic study. Once known, the patient's distribution and elimination kinetics can then be used to extract the absorption profile from a subsequent transdermal pharmacokinetic study. Knowledge of the rate of absorption of fentanyl into the systemic circulation is important in predicting the clinical efficacy and possible toxicity of a transdermal fentanyl system. Bioavailability of a drug is defined as the fraction of an administered dose that reaches the systemic circulation.⁷ Metabolism of fentanyl in the skin or degradation by the skin's bacterial flora may reduce the amount of fentanyl reaching the systemic circulation after a transdermally administered dose.^{8–10} The objective of this study was to determine the absorption characteristics and systemic bioavailability of fentanyl administered by a transdermal delivery system with a predicted nominal delivery rate of $100 \mu\text{g/h}$.

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Methods

PATIENTS

After approval of the study protocol by the Stanford University panel on Human Subjects in Medical Research, eight patients (five female, three male) were selected for study. Average age of the subjects was 45 yr (range 33–57 yr) and average weight was 68 kg (range 52–100 kg). Requirements for study inclusion were: 1) the need for surgery requiring general anesthesia lasting 3 h or more to assure the return of spontaneous ventilation after an infusion of fentanyl; 2) a surgical procedure associated with significant postoperative pain; 3) an anticipated hospital stay of at least 4 days after surgery for completion of the transdermal pharmacokinetic study; and 4) a normal hematocrit in order to tolerate withdrawal of multiple blood samples. Patients with a history of hepatic disease or drug sensitivity to an agent in the study protocol were excluded. All patients were undergoing major spine surgery (seven lumbar laminectomies with Knodt rod fusions, one cervical fusion).

Patients were fasted prior to surgery and brought to the operating room after premedication, if clinically indicated, with midazolam and/or morphine. A peripheral iv catheter was inserted for fluid and drug administration and a 20-gauge catheter inserted in a radial artery for blood sampling and blood pressure monitoring.

Patients breathed oxygen for at least 3 min and were given 1 mg of pancuronium to attenuate fentanyl-induced muscular rigidity and bradycardia. An infusion of fentanyl, 150 μ g/min for 5 min (seven patients) or 6.5 min (one patient), was administered. One minute after termination of the fentanyl infusion, general anesthesia was induced with thiopental. Further muscle relaxant was given, ventilation was controlled, and tracheal intubation was performed 2–3 min after the termination of the fentanyl infusion. General anesthesia was maintained with 70% nitrous oxide with a volatile agent added as needed (typically at 0.25–0.50 MAC concentrations).

Postoperatively, patients received parenteral morphine (six patients) or meperidine (two patients) for analgesia *via* a patient-controlled analgesic infusion device (five patients) or intramuscular injection (three patients). On the first postoperative day (24 h after the iv dose of fentanyl), a transdermal fentanyl delivery system was placed on the patient's upper anterior chest and left in place for 24 h.

The patient's respiratory rate, blood pressure, and heart rate were monitored and recorded at 4-h intervals throughout the transdermal study. Any signs or symptoms suggestive of adverse reaction to the transdermal fentanyl system were recorded. The skin site was examined at the time of removal of the system and again 24 h later for any sign of reaction.

BLOOD SAMPLING

Blood samples for the intravenous pharmacokinetic portion of the study were drawn before and 2, 3, 4, 5, 6, 7, 8, 10, 15, 30, 45, 60, 90, 120, 180, 240, 360, 480, 720, 960, 1200, and 1440 min after the start of the fentanyl infusion. Samples were drawn from the arterial catheter for the first 6–8 h after the fentanyl infusion. Subsequent samples were drawn from either a central venous catheter or a 16-gauge peripheral iv catheter inserted in the left external jugular vein. Venous blood sampling during the transdermal portion of the study was at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 30, 36, 48, 60, and 72 h after system placement. Blood samples were allowed to clot, then centrifuged, and the serum collected. The serum samples were frozen at -20°C until performance of the fentanyl assay.

FENTANYL ASSAY

Serum fentanyl concentrations were determined by gas chromatography with mass spectroscopy detection (GC/MS) sensitive to 0.2 ng/ml with a mean coefficient of variation of 6.9% over the range of 0.2–68 ng/ml. Extraction of fentanyl from serum was accomplished by basifying the serum and addition of 5% isopropyl alcohol/N-butyl chloride. This mixture was then vortexed, centrifuged, and the organic layer evaporated under nitrogen to dryness. The fentanyl residue was reconstituted with toluene and injected into the GC/MS system. The mass spectrometer used was a Hewlett-Packard 5987 GC/MS fitted with a Durabond[®] methylsilicone capillary column, 30 m \times 0.25 mm (I.D.), with a film thickness of 0.25 micron from J&W Scientific. The oven temperature program was 150°C (hold 1.00 min) with a $30^{\circ}/\text{min}$ ramp to 300°C (hold 3.00 min). The injector temperature was 280°C . Operating conditions in the positive electron ionization mode were: ionization energy, 70 eV; source temperature, 200°C . The ions scanned were 245.0 for fentanyl and 86.0 for flurazepam, the internal standard.

The residual fentanyl content of the transdermal system, after removal from the patient, was measured by a high-pressure liquid chromatography (HPLC) technique. Residual fentanyl was extracted from the spent transdermal system with 50:50 acetonitrile:0.02 normal sulfuric acid. The HPLC system used was a Waters Wisp[®] 710A injector, a Waters 6000A pump with a flow rate of 1.0 ml/min, a Rainin microsorb C-18, 250 \times 4.6 mm, 5 micron particle size, and a Schoeffel variable wavelength detector model 769 set at 210 nm. The mobile phase was 50:50 acetonitrile:water with final concentrations of 0.1% (W/V) octanesulfonic acid and 0.1% (V/V) triethylamine.

PHARMACOKINETIC ANALYSIS

For both the iv and transdermal portions of the study, the area under the serum fentanyl concentration *versus*

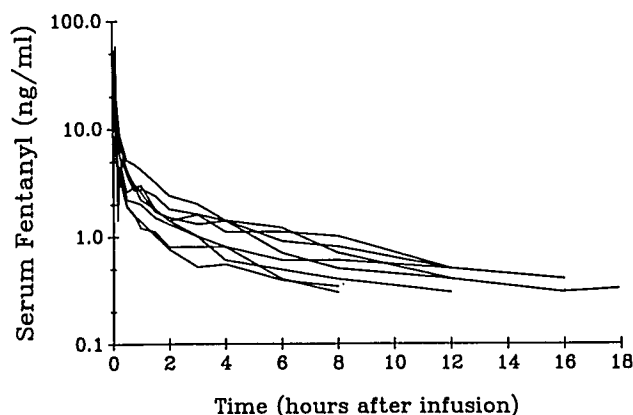


FIG. 1. Measured serum fentanyl concentrations for each of the eight patients after the intravenous fentanyl infusion.

time profile (AUC_{IV} and AUC_{TTS} , respectively) from the time of administration of the dose to the last measurable concentration point was calculated using the linear trapezoidal method.⁷ The extrapolation to infinity was calculated by dividing the last measurable serum concentration by the first-order rate constant of the terminal phase of the profile. This first-order rate constant was determined using linear regression on the log-transformed serum fentanyl concentration data from the terminal log-linear phase of the serum concentration profile. The sum of these two components was the estimate of the total area under the curve.

The clearance of fentanyl was calculated as the ratio of the iv dose and AUC_{IV} . The amount of fentanyl delivered was determined as the difference between the initial transdermal system content and the residual content measured after removal from the patient at 24 h. The amount of fentanyl absorbed from the transdermal system was calculated as the product of clearance and AUC_{TTS} .

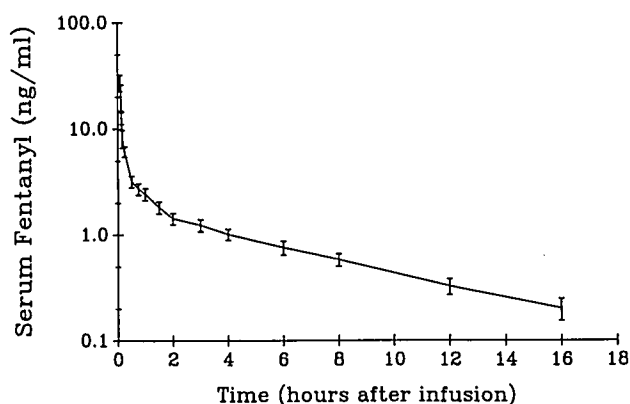


FIG. 2. Mean and SEM of the study group's serum fentanyl concentrations after the intravenous fentanyl infusion.

The bioavailability was calculated as the ratio of the total amount of fentanyl absorbed and the amount delivered. The individual bioavailabilities were then averaged and their standard deviation calculated.

To determine the transdermal fentanyl absorption profile for each patient, the three-compartment Loo-Riegelman method was used.¹¹ The three-compartment Loo-Riegelman method is an analytic deconvolution technique that uses the serum concentrations from the iv portion of the study to extract absorption information from serum concentrations measured after administration of the drug by the transdermal route. Each patient's concentration versus time profile following iv administration of fentanyl was fit to a triexponential equation using a nonlinear least squares fitting program, PCNONLIN.^{**} The data points were weighted by the reciprocal of the square of the observed serum concentration (weighted least squares). This fit was then used to supply the pharmacokinetic parameters needed for the equations in the Loo-Riegelman absorption calculations. For each sampling time during the transdermal portion of the study, the population mean absorption rate and standard error of the mean was calculated. Systemic bioavailability was calculated again using the Loo-Riegelman estimate of the total dose of fentanyl absorbed during the transdermal study. The amount of fentanyl remaining to be absorbed at 24 h was calculated as the total dose absorbed minus the dose absorbed between 0 and 24 h. This represents fentanyl that reached the systemic circulation after the transdermal system was removed.

Results

Figure 1 shows the measured serum fentanyl concentrations for the individual patients in the iv pharmacokinetic study, while figure 2 summarizes the mean data of the group. The distribution and elimination phases were well characterized with the blood sampling protocol used. In all but one patient, serum fentanyl concentrations were below the limits of assay detection after the 16-h sample. Table 1 presents the pharmacokinetic parameters obtained from the iv portion of the study along with two other published parameter sets for comparison.^{12,13}

The serum fentanyl concentrations from each patient obtained after placement of the transdermal fentanyl system are shown in figure 3 and the mean data in figure 4. Serum fentanyl concentrations gradually increased during the first 14 h after placement of the system, were relatively constant from 14 h to 24 h at 1.8 ± 0.8 ng/ml (mean \pm SD of six samples from each of the eight patients), and

^{**} Metzler CM, Weiner DL: PCNONLIN User's Guide. Statistical Consultants, Inc., 1986.

TABLE 1. iv Fentanyl Pharmacokinetic Parameters (Mean \pm SD) with Two Previously Published Parameters Sets for Comparison

	Present Study	Scott and Stanski ¹⁵	McClain and Hug ¹⁸
Rapid distributional half-life (min)	1.35* \pm 0.77	1.0* \pm 0.6	1.65* \pm 0.22
Slow distributional half-life (min)	24.7* \pm 27.7	18.5* \pm 11.9	12.7* \pm 3.1
Elimination half-life (min)	428* \pm 239	475* \pm 193	241* \pm 66
Vc (l)	15.9 \pm 8.9	12.7 \pm 5.9	26.6 \pm 9.8
Vdss (l)	398 \pm 163	339 \pm 139	311 \pm 36
Clearance (l/min)	0.77 \pm 0.33	0.57 \pm 0.21	0.88 \pm 0.17

* Harmonic mean.

fell slowly after system removal at 24 h. The terminal half-life after removal of the system was 17.0 ± 2.3 h.

Figure 5 indicates the rate of absorption ($\mu\text{g/h}$) of fentanyl into the systemic circulation for the study group calculated by the Loo-Riegelman method. The rate of absorption increased during the initial 4–8 h, remained relatively constant at $91.9 \pm 25.7 \mu\text{g/h}$ until 24 h, and decreased gradually after transdermal system removal at 24 h. The terminal half-life of the rate of absorption after removal was 16.6 ± 3.7 h.

Table 2 indicates: 1) the dose delivered from the transdermal system; 2) the total amount of drug absorbed into the systemic circulation; 3) the bioavailability of transdermally administered fentanyl, and; 4) the amount of fentanyl remaining to be absorbed at 24 h. Total drug reaching the systemic circulation and bioavailability were calculated using two methods: a) the model-independent ratio of dose-normalized AUCs and; b) the model-dependent Loo-Riegelman method. The two methods of calculating bioavailability produced similar results with a value of 0.92 ± 0.33 from the model-independent method and 0.92 ± 0.37 from the model-dependent method.

No significant adverse effects were attributed to the use of transdermal fentanyl in this study group. There were no instances of respiratory depression, urinary re-

tention, pruritus, or local skin reaction. Six of the eight patients complained of nausea during the study. Four of these patients complained of nausea prior to placement of the transdermal fentanyl system and a fifth had nausea related to a headache caused by a dural tear sustained during surgery.

Discussion

Transdermal administration of a drug offers several advantages over other routes of drug delivery, but also presents unique concerns. Discussion of these advantages and concerns requires a brief review of transdermal delivery system construction and drug absorption mechanisms.

Figure 6 is a schematic representation of a transdermal drug delivery system similar to the one used in this study.^{2,14} The backing prevents drug from being lost into the environment and prevents water from entering the drug reservoir. The reservoir contains a supply of drug appropriate for the predetermined functional life of the system. The next layer is a microporous membrane that controls the rate of release of drug from the reservoir. The contact adhesive holds the system in place, and may also provide for initial rapid absorption of drug if the

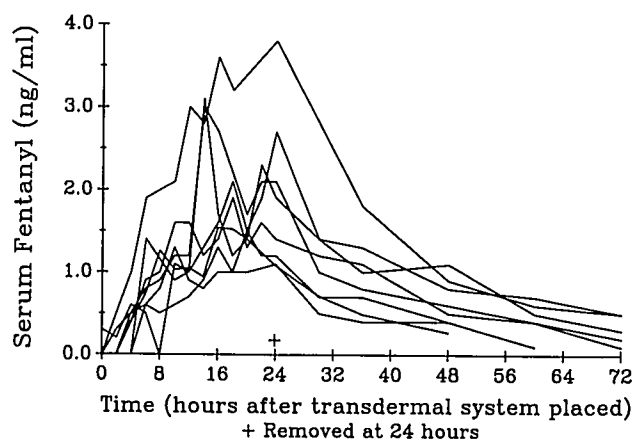


FIG. 3. Measured serum fentanyl concentrations for each of the eight patients after placement of the transdermal fentanyl system.

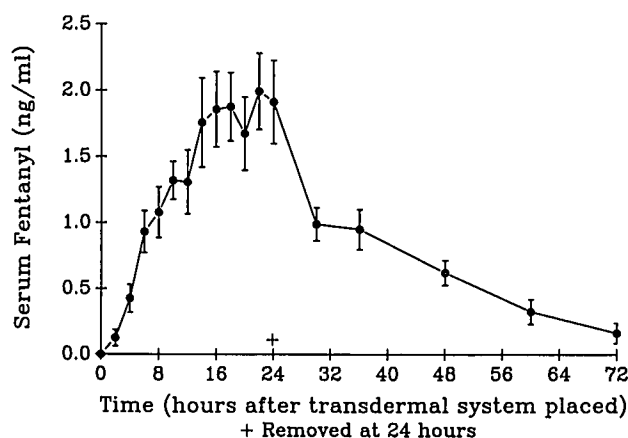


FIG. 4. Mean and SEM of the study group's serum fentanyl concentrations measured during the transdermal pharmacokinetic study.

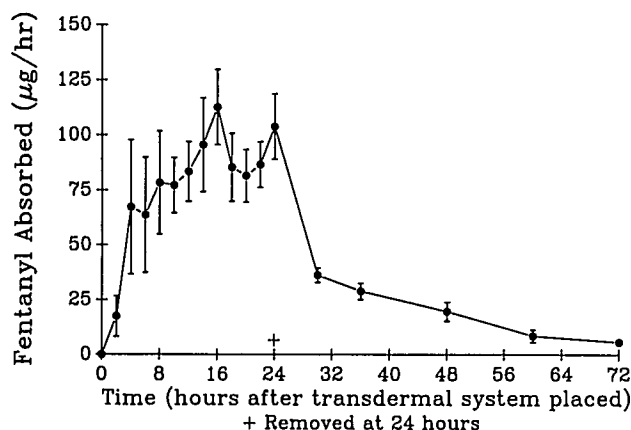


FIG. 5. Mean and SEM for the study group's rate of absorption of fentanyl into the systemic circulation after placement of the transdermal fentanyl system. Calculated using the three-compartment Loo-Riegelman method.

adhesive itself contains drug. Release of drug from this system is characterized by two phases: an initial phase with rapid skin absorption of the drug in the contact adhesive, and a plateau phase with constant, sustained release of drug from the reservoir.

Transdermal drug absorption has been recently reviewed.⁸ Drug moves from the reservoir to the system-stratum corneum interface, crosses to the stratum corneum, passively diffuses through the keratinous layers of the stratum corneum, enters into the viable epidermis, and passively diffuses through the viable epidermis to the dermis where the drug is removed *via* the cutaneous microcirculation. The rate-limiting step in absorption is the passive diffusion through the lipophilic, keratinous stratum corneum. Permeability of the stratum corneum varies widely and is affected by site on the body, skin tempera-

ture, skin blood flow, ethnic group, sweat gland function, presence or absence of suntan, and stratum corneum damage due to disease, chemicals, or excessive hydration. Occlusion of the skin surface, such as seen with placement of a transdermal drug delivery system, may increase permeability 200–300% due to changes in skin temperature and hydration.

Drug transfer from the drug reservoir to the systemic circulation is limited by the slowest step in the absorption pathway. The rate-controlling membrane in the transdermal fentanyl system is designed to release drug more slowly than the rate of absorption through the most impermeable stratum corneum. Ideally, this allows the overall control of drug absorption to reside in the design of the transdermal system and not be dependent upon the widely variable permeability of the stratum corneum.

Although the rate of drug release from the transdermal system can be controlled, there is no guarantee that all drug released will reach the systemic circulation. Drug may be degraded by the bacterial flora of the skin or may undergo "first-pass" metabolism as it passes through the epidermis and dermis. Wester *et al.*¹⁵ demonstrated that 15–20% of nitroglycerin absorbed transdermally by rhesus monkeys undergoes cutaneous first-pass metabolism. Approximately 40% of topically applied testosterone underwent first-pass cutaneous metabolism in a mouse skin model.¹⁰ In the present study, average bioavailability was 0.92, indicating that transdermally administered fentanyl is neither significantly degraded by the skin's bacterial flora nor susceptible to significant first-pass cutaneous metabolism.

One advantage of transdermal drug administration is the ability to maintain a relatively constant serum drug concentration for a prolonged period of time. The present study demonstrates this desirable characteristic for the

TABLE 2. Transdermal Absorption Characteristics

Patient	Dose Delivered (mg)	Dose-normalized AUCs		Three-compartment Loo-Riegelman		
		Dose Absorbed (mg)	Bioavailability	Dose Absorbed (mg)	Bioavailability	Amount (mg) in Depot at 24 h
1	4.75	3.30	0.70	3.19	0.67	0.61
2	2.32	3.39	1.46	3.49	1.50	1.56
3	4.28	4.21	0.98	4.37	1.02	1.52
4	3.51	2.91	0.83	3.27	0.93	1.24
5	2.48	3.43	1.38	3.49	1.41	1.62
6	3.17	2.28	0.72	2.06	0.65	0.87
7	3.94	2.23	0.57	1.88	0.48	0.57
8	2.83	1.98	0.70	2.06	0.73	0.61
Mean	3.41	2.97	0.92	2.98	0.92	1.07
SD	0.88	0.76	0.33	0.88	0.37	0.43

Dose delivered = total amount of fentanyl lost from the transdermal system determined by residual analysis after removal of system at 24 h. Total fentanyl absorbed and bioavailability calculated by two methods: a) dose-normalized AUCs (model independent) and, b) three-

compartment Loo-Riegelman method (model dependent). Dose in depot at 24 h = amount of fentanyl that will reach the systemic circulation after the system is removed.

transdermal fentanyl system. The serum fentanyl concentration rose gradually during the first 12–14 h after system placement and remained relatively constant until removal at 24 h. As serum fentanyl levels are quite low for a number of hours after placement of the transdermal system, it would be reasonable to place the system prior to surgery and provide anesthesia/analgesia by parenterally administered opioids for the first few hours after system application.

In the study group, analgesia was provided parenterally (via PCA infusion or im injections) throughout the study in amounts sufficient to provide adequate patient analgesia. Serum fentanyl concentrations were 1.8 ± 0.8 ng/ml during the 14–24-h sample period. This concentration range is appropriate for postoperative analgesia and low enough to minimize side effects. Other investigators have demonstrated the decreased narcotic requirement with use of this transdermal fentanyl system.^{6,16}

As figure 3 demonstrates, interindividual variability in serum fentanyl concentrations is significant following placement of the transdermal fentanyl system. This variability is partially due to the large interindividual variability in iv fentanyl pharmacokinetics^{12,13,17} and partially due to interindividual variability in transdermal absorption characteristics. Table 1 contains the pharmacokinetic values obtained from the iv portion of this study along with values from the previously published studies of McClain and Hug¹² (in unanesthetized volunteers) and Scott and Stanski¹³ (in anesthetized patients). The mean values from this study are similar to these previous studies. Interindividual variability was somewhat greater among our patients. If fentanyl had been infused intravenously in these patients at a constant rate of 90 μ g/h (the average absorption rate from the transdermal system during the "plateau" period of absorption), the average serum fentanyl concentration for the study group would have been 1.9 ng/ml, with a 90% confidence interval for individual serum concentrations being 1.4–5.6 ng/ml (based on measured interindividual variability in clearance in these patients). Thus, the observed average concentration with the transdermal system of 1.8 ng/ml with a 90% confidence interval for individual serum concentrations of 0.5–3.1 ng/ml is comparable to that which would be expected from a constant iv infusion in these patients.

Serum fentanyl concentrations fell in a log-linear manner after removal of the transdermal system. This terminal phase had an average half-life of 17 h, similar to that found in another recent study.⁶ The terminal half-life of fentanyl after the iv dose averaged 6.1 h, indicating that the much longer terminal phase seen after transdermal system removal is reflecting slow, continued absorption from a peripheral reservoir. This peripheral reservoir most likely represents the stratum corneum at the site of the recently removed transdermal system.

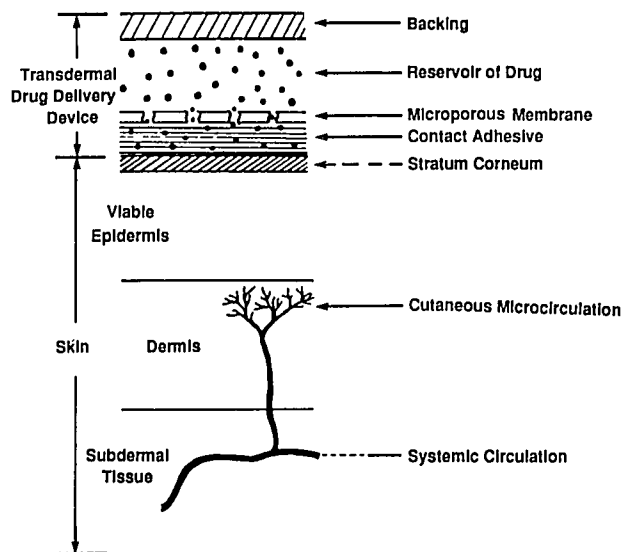


FIG. 6. Diagram of the TTS-100 transdermal fentanyl delivery system.

There are several concerns regarding the present study. Mean population bioavailability was quite well determined with this sample size, but the rate of absorption from the transdermal system had considerable variability. A larger sample size would better characterize the average absorption rate for the transdermal fentanyl system. Determination of systemic bioavailability requires an accurate estimate of the initial fentanyl content in the transdermal system in order to obtain an accurate estimate of the dose of transdermal fentanyl delivered. It is not possible to assay fentanyl content in a particular system prior to its application on the patient; therefore, there is some error inherent in the calculation of delivered dose. Sampling of ten transdermal fentanyl systems showed the mean and standard deviation of initial fentanyl content to be 10.2 ± 0.4 mg. The patients studied were generally healthy and were not taking medications known to influence fentanyl kinetics. Extrapolation of our results to other patient groups having altered fentanyl kinetics may be unwarranted.

It is interesting to note that two patients in the study group had an apparent transdermal fentanyl bioavailability greater than 1.0, a value that seems to contradict the definition of bioavailability. Bioavailability was calculated as the transdermal dose absorbed into the systemic circulation divided by the fentanyl content lost from the transdermal system. If the absorbed transdermal dose is overestimated, or the loss of fentanyl from the transdermal system underestimated, the calculated bioavailability may be greater than 1.0. The transdermal dose absorbed was calculated as the product of AUC_{TTS} and Cl_{IV} , either of which may contain error causing our estimate of the

transdermal dose absorbed to be either higher or lower than the true value. The amount of fentanyl lost from the transdermal system is calculated as initial fentanyl content minus residual content. The initial fentanyl content is not known exactly, it must be estimated by sampling of other transdermal systems manufactured by the same process and, thus, this value contains some error. As the measurement of residual fentanyl content also contains some error inherent to the assay process, the calculation of transdermal dose delivered is an estimate which may actually over- or underestimate the true transdermal dose delivered. There is no reason to suspect these estimates of AUC_{TTS} , Cl_{IV} , and initial and residual transdermal system fentanyl content of being systematically biased (except for Cl_{IV} as discussed below). Thus, the estimate for bioavailability in each patient should be unbiased, although it may be higher or lower than the "true" value of bioavailability in each patient. The calculated estimate of bioavailability in a single patient may certainly be greater than 1.0, depending on the actual estimates for AUC_{TTS} , Cl_{IV} , and the amount of fentanyl lost from the transdermal system. In fact, if the true bioavailability of transdermal fentanyl were 1.0, we would expect fully half of our study group to have estimates of bioavailability which were greater than 1.0. If we exclude those patients having calculated bioavailabilities greater than 1.0, we introduce significant bias into our estimate of population bioavailability, obtaining a falsely low value.

An important assumption in the design of this study was that fentanyl clearance would not change from the intravenous study to the transdermal study. General anesthesia may be associated with a decrease in hepatic blood flow or enzyme activity and might be expected to decrease fentanyl clearance. Had this occurred, it would have resulted in a falsely low calculated bioavailability. As average bioavailability in this study was close to 1.0, decreases in fentanyl clearance during the first 24 h of the study (which included the period of general anesthesia and the first 18–21 h after surgery) appear to have not been significant.

Transdermal administration of fentanyl is simple, convenient, and allows prolonged use of a potent, short-acting opioid. The initial time lag of 10–14 h in obtaining analgesic serum fentanyl concentrations after placement of the system suggests that the system either be placed prior to surgery, or that parenterally administered opioids be used for analgesia during the first few hours after surgery. After the initial lag, serum fentanyl concentrations were maintained at a level appropriate for postoperative analgesia, 1.8 ± 0.8 ng/ml, until the system was removed at 24 h. The interindividual variability in serum fentanyl concentrations following placement of the transdermal system was comparable to that expected from a constant rate iv infusion of fentanyl in these patients. This variability necessitates the same monitoring for opioid side

effects when using this transdermal fentanyl system as needed when using parenteral routes for opioid administration. Serum fentanyl concentrations decrease very slowly (half-life 17.0 ± 2.3 h) following removal of the transdermal system. This is due to continued absorption of fentanyl from a peripheral depot of drug. Transdermal administration of fentanyl appears to provide a convenient means of obtaining relatively constant analgesic serum concentrations of fentanyl for considerable periods of time in the postoperative patient.

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