Anesthesiology
78:36–43, 1993

Transdermal Fentanyl for Cancer Pain

Repeated Dose Pharmacokinetics

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Background: **The transdermal therapeutic system (fentanyl), or TTS(fentanyl), continuously delivers fentanyl for up to 72 h. The transdermal therapeutic system (fentanyl)-100 delivers approximately 100 μg/h. The repeated dose pharmacokinetics of this drug using the recommended dosing interval have not been evaluated previously and were determined in the present study.**

Methods: **Blood samples were obtained from ten opioid-tolerant cancer patients who received five applications of TTS(fentanyl) at 72-h intervals. A sample of venous blood was taken before each dose; multiple samples were taken during and after the fifth application. A gas chromatographic/mass spectrometry method was used to assay fentanyl (limit of detection 0.2 ng/ml).**

Results: **For the fifth dose, the mean (SD) maximum concentration was 2.6 (1.3) ng/ml and the mean (SD) area under the serum fentanyl concentration-time curve (0–72 h) was 116.9 (59.9). Following removal of the system, the mean (SD) apparent half-life was 21.9 (8.9) h. There were no differences among the serum fentanyl concentrations measured before the second through fifth doses. Fentanyl absorption was 47% complete at 24 h, 88% complete at 48 h, and 94% complete at 72 h. The mean (SD) dose delivered during the 72-h period was 4.3 (1.1) mg. A first-dose trough concentration predicted from fifth-dose kinetics and the actual first-dose trough concentration were very similar. Adverse effects ascribed to the transdermal system were minimal.**

Conclusions: **These results suggest that steady-state serum concentrations are approached by the second dose of TTS(fentanyl) and that the kinetics are stable with repeated dosing. The apparent half-life following system removal is relatively long, indicating ongoing absorption from a subcutaneous depot. (Key words: Analgesics, opioid: fentanyl. Anesthetic techniques: transdermal. Pain, chronic: cancer. Pharmacokinetics: transdermal fentanyl.)**

Received from the *Pain Service, Department of Neurology, Memorial Sloan-Kettering Cancer Center; †ALZA Corporation, Palo Alto, California; and ‡Department of Pharmacology, Cornell University Medical College, New York, New York. Accepted for publication September 26, 1992. Supported by a grant from Janssen Research Foundation, Titusville, New Jersey, grant CA-32897 from the National Cancer Institute, and grant JFRA-244 from the American Cancer Society.

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LONG-TERM, regular administration of an opioid is a highly effective approach for the treatment of cancer pain. The oral route of administration is preferred, but a substantial proportion of patients, particularly those with pain associated with progression of the cancer, require parenteral administration.[1] Numerous methods of opioid delivery have been developed to meet the analgesic requirements of these patients. A recent advance is the development of a transdermal therapeutic system for the opioid agonist, fentanyl, or TTS(fentanyl; ALZA Corporation, Palo Alto, CA, and Janssen Pharmaceutica, Titusville, NJ), which delivers the opioid continuously through the skin. This system is available in four dosage strengths that vary in drug delivery rate from 25 μg/h [TTS(fentanyl)-25] to 100 μg/h [TTS(fentanyl)-100].

The TTS(fentanyl) system has been evaluated in controlled trials of patients with postoperative pain.[2,3] Although experience with chronic administration is limited,[4,5] survey data acquired in the cancer population suggest that most chronic pain patients treated with these systems will be able to maintain clinical effects over a dosing interval of 72 h. The pharmacokinetics of one or two doses of the TTS(fentanyl) system have been evaluated extensively,[6–10] but there have been no repeated-dose pharmacokinetic studies using the 72-h dosing regimen that appears suitable for clinical use. Repeated dose pharmacokinetics at this dosing interval are needed to evaluate the stability of drug delivery and metabolism during long-term use. To obtain this information, serum fentanyl concentrations were measured in cancer pain patients who received five consecutive applications of TTS(fentanyl) at 72-h dosing intervals.

Methods and Materials

This investigation was an open-label, repeated-dose pharmacokinetic study of TTS(fentanyl)-100, which delivers fentanyl at approximately 100 μg/h. Permission for the study was granted by the Institutional Review Board of Memorial Sloan-Kettering Cancer Center. Patients gave informed consent prior to participation in the study.

Patients and Dosing Regimen

Candidates for the study were adult inpatients and outpatients who were receiving an opioid for chronic cancer pain at a dose equivalent to or greater than 53 mg intramuscular morphine daily. Calculated equivalences were based on widely published relative potencies among opioid drugs.[11] Patients were excluded if life expectancy was less than 45 days, active skin disease was present, or there was a history of any significant renal, hepatic, pulmonary, or hematologic disease.

Each patient applied one TTS(fentanyl)-100 system every 3 days for 15 days (five systems). Each system was applied to a different area of the torso. Other opioid drugs were continued, and patients were reassessed frequently by a nurse observer, who determined the need for reduction in the previous analgesic dosing regimen, recorded vital signs prior to each dose and elicited reports of adverse effects.

Patients who completed the pharmacokinetic study were given the option of continuing in an open-label extension protocol. Those who agreed were provided the transdermal fentanyl system on a regular basis. Adverse experiences were recorded during this extension period.

Blood Sampling and Analysis

Single 5-ml venous blood samples were drawn immediately before the application of the first through fifth doses. After the fifth system was applied, blood was sampled at hours 1, 2, 4, 6, 8, 12, 16, 24, 32, 48, 56, and 72. Following removal of the fifth system, blood was sampled at hours 8, 24, 32, 48, and 72.

Blood samples were centrifuged immediately following collection. Serum was frozen at −20° C and shipped on dry ice to ALZA Corporation for assay. Fentanyl was first extracted from the serum and then assayed using a gas chromatographic/mass spectrometry method.[10] For the extraction, 5% isopropyl alcohol/N-butyl chloride was added to basified serum and the organic layer was evaporated from the centrifuged solution under nitrogen. The fentanyl residue was redissolved in toluene. This solution was assayed using a Hewlett-Packard 5987 system fitted with a Durabond methylsilicone capillary column (J & W Scientific, Folsom, CA), which was 30 × 0.25 mm and had a film thickness of 0.25 μ. The oven temperature was programmed to begin at 150° C (for 1.0 min), increased 30° C per minute to 300° C, then held at the highest temperature for 3.0 min. The temperature of the injector was 280° C. In the positive electron ionization mode, the ionization energy was 70 eV, and the source temperature was 200° C. The ions scanned were 245.0 for fentanyl and 86.0 for the internal standard, flurazepam. The minimum detection limit of fentanyl in this assay was 0.2 ng/ml (mean coefficient of variation 6.9% over a range of 0.2–68 ng/ml).

After the 72-h application, each transdermal system was shipped to ALZA Corporation for assay of residual fentanyl. Assay procedures were validated previously by this laboratory. The drug was extracted from the system and measured using a high-pressure liquid chromatography method. Extraction was accomplished by immersing each system in a solution of 50:50 acetonitrile:0.02 normal sulfuric acid. The high-pressure liquid chromatography method employed a Waters Wisp 710A injector (Milford, MA); a Waters 6000A pump that had a flow rate of 1.0 ml/min; a Rainin microsorb C-18 (Woburn, MA), 250 × 4.6 mm, 5-μ particle size; and a Schoeffel variable wavelength detector model 769 (Westwood, NJ) set at 210 nm. The mobile phase of 50:50 acetonitrile:water had final concentrations of 0.1% (W/V) octanesulfonic acid and 0.1% (V/V) triethylamine.

Data Analysis

Serum fentanyl concentration-time profiles were generated for each patient. Concentrations below the detection limit of the assay were assigned a value of 0 for the pharmacokinetic calculations.

The pharmacokinetic profile obtained during and following the application of the fifth system was analyzed for routine pharmacokinetic parameter estimates, including minimum and maximum concentration, area under the serum fentanyl concentration-time curve (AUC), and apparent elimination rate constant (K). The apparent elimination rate constant was estimated by linear regression of log-transformed serum fentanyl concentrations following removal of the fifth system.

The apparent half-life for fentanyl was calculated as 0.693/K.

The linear trapezoidal method was used to calculate the AUC from 0 to 72 h (AUC_{0-72}) and from 0 h until serum fentanyl concentration became undetectable (AUC_t). An AUC from 0 h to infinity (AUC_{inf}) was estimated as the sum of the AUC_t and the area extrapolated from C_t (C_t divided by K). To confirm that steady state had been approached by the fifth application, AUC_{inf} values were corrected for initial concentration present in serum before the fifth application by subtracting the area corresponding to C_0/K for that interval, and this value was compared to the AUC_{0-72}.

To evaluate the time to approach steady state and the potential for drug accumulation, the mean serum fentanyl concentrations obtained from the single samples taken immediately prior to the second through fifth applications were compared. Two-tailed, paired *t* tests were used to evaluate differences between each pair of mean concentrations. These values also were analyzed for intersubject and intrasubject variability using an analysis of variance model and an analysis of the interaction between the dose number and concentration (a "dose number effect"). Statistical significance was set a $P < .05$.

The dose delivered by each system was calculated from the residual content of fentanyl following 72 h of application. Using the Wagner-Nelson method,[12] the cumulative fentanyl fraction absorbed was calculated to estimate the amount of drug absorbed at each time point during the course of a single TTS application. The total amount of the drug absorbed represents the amount of drug in the body plus the drug that has been eliminated. The Wagner-Nelson method was used for this analysis, despite the possibility that it would introduce some error since it assumes a one-compartment model rather than the three-compartment model that better describes fentanyl, because intravenous kinetic data were not available for these patients and other modeling techniques would have required this information.

The possibility of changes in pharmacokinetics with repeated dosing was assessed by simulating a single application serum concentration profile based on fifth-dose data and comparing the predicted concentration at 72 h to the actual serum concentration measured 72 h after application of the first system. The model used to simulate first-dose data from the fifth-dose pharmacokinetic profile was based on the superposition principle. Using the K for each subject, the contribution from the fourth application was subtracted from the concentrations measured during the fifth application. The predicted 72-h serum fentanyl concentration was compared to the actual concentration using a two-tailed *t* test. Statistical significance was set at a *P* value of $<.05$.

Results

Thirteen patients were entered in the trial. One patient was withdrawn prior to application of the first system because of the inability to monitor his progress in the home. Two patients were withdrawn from the trial during the period of drug administration. One patient was discontinued from the trial on the first day because of an intercurrent pneumonia; the other was discontinued on the 14th day because of an inadvertent removal of the transdermal system. Ten patients, five men and five women, completed the study. Demographic and tumor-related data for these patients are described in table 1.

The serum concentration profile during the fifth dose is displayed in figure 1, and the pharmacokinetic parameter estimates derived from this profile appear in table 2. The mean (SD) serum concentration achieved in each patient during the 72-h dosing period was 1.6 (0.8) ng/ml, and the mean (SD) C_{max} was 2.6 (1.3) ng/ml. The mean (SD) AUC_{0-72} was 116.9 (59.9) ng-h/ml and the mean (SD) AUC_{inf} was 113.2 (70.3) ng-h/ml. Following removal of the system, serum fentanyl concentrations declined with a mean (SD) apparent half-life of 21.9 (8.9) h.

The percent fentanyl dose absorbed was calculated during application of the fifth system (fig. 2). This calculation was performed on eight patients, since a single measurement in each of two cases was spuriously low and resulted in skewing of the cumulative absorption. Fentanyl absorption was 47% complete at 24 h, 88% complete at 48 h, and 94% complete at 72 h.

The mean (SD) serum fentanyl concentration at hour 72 following the first dose (prior to application of the second system) was 1.2 (0.8) ng/ml. The mean (SD) pre-application serum fentanyl concentration for the subsequent doses increased to a maximum of 1.4 (0.8) ng/ml (fig. 1). The change from the beginning of the second dose to the beginning of the fifth dose was not statistically significant in the analysis of variance ($P = .78$) or the analysis of a "dose number effect" ($P = .19$). A power analysis was applied to these nonsignificant results and revealed that the power to detect

Table 1. Demographics, Tumor Type, and Drug Use Among Study Patients

Subject No.	Sex	Age (yr)	Weight (kg)	Height (cm)	Cancer Diagnosis	Opioid*	Opioid Dose (mg/day)†	Other Drugs‡
1	F	67	63.6	157.5	Breast	Morphine	800	Acetaminophen Choline Mg trisalicylate
2	F	67	52.7	162.6	Colon	Hydromorphone	256	Acetaminophen Methylphenidate Dexamethasone Chloropromazine
3	F	65	53.6	45.0	Breast	Morphine	240	Choline Mg trisalicylate
4	F	34	53.6	170.2	Colon	Levorphanol Hydromorphone	661	Dexamethasone
5	M	62	67.3	172.7	Lung	Morphine	140	Choline Mg trisalicylate Acetaminophen Amitriptyline
6	F	60	77.7	157.5	Colon	Levorphanol	150	—
7	M	50	64.5	172.7	Colon	Morphine	1440	—
8	M	64	88.6	180.3	Lung	Morphine	540	Dexamethasone
9	M	48	54.5	160.0	Lung	Morphine	780	Amitriptyline
10	M	63	38.2	157.5	Lung	Morphine	300	Acetaminophen Haloperidol
Mean	—	58.0	60.6	164.6	—	—	—	—
SD	—	11.3	15.9	9.2	—	—	—	—

* Opioid prescribed on a regular schedule during the study period.

† Doses of the opioid and other drugs changed during the study period in response to the clinical condition of the patient. The largest dose administered on a regular basis is indicated with the quantity expressed as milligrams equivalent to im morphine, calculated from standard relative potency tables.

‡ Other drugs prescribed on a regular schedule during the study period.

the observed maximal difference between the concentration prior to the second dose and the concentrations prior to any subsequent dose was 57%. This limited power reflects the small sample size in this study and indicates that the lack of statistically significant differences in the trough concentrations should be viewed as suggestive, but not conclusive, evidence that steady-state concentrations were approached by the second application of TTS(fentanyl).

The trough serum concentrations also were assessed for intrasubject and intersubject variability. Across patients, the mean difference between the highest and lowest of each trough concentration (prior to the second through fifth applications) was 6.6 ng/ml, and the coefficient of variation was 50.7%. Within subjects, the mean difference between the highest and lowest values was 2.4 ng/ml, and the coefficient of variation was 34.4%, or 67% less than the intersubject variability.

Measurement of residual fentanyl following a 72-h application revealed that the mean (SD) dose delivered by all systems used in the study was 4.3 (1.1) mg and the overall coefficient of variation for the dose delivered was 26.9%. There was no significant change in the mean dose delivered over time, and the coefficient of variation in the dose delivered to individual patients ranged from 13.0% to 33.7%.

The simulated serum concentration profile generated to reflect the kinetics of a single dose is depicted in figure 3. The predicted serum concentration at hour 72 was not significantly different ($P = .32$) from the value actually measured 72 h after the first application. As discussed previously, this study had limited power to detect statistically significant differences, and consequently, this finding of no difference should be considered as suggestive, but not conclusive, evidence that kinetics were stable between the first and fifth applications of the transdermal system.

All study patients had advanced cancer and most symptoms reported during the study were attributable to the underlying medical condition. Although all patients were opioid tolerant, some experienced an exacerbation of opioid-related side effects that could be

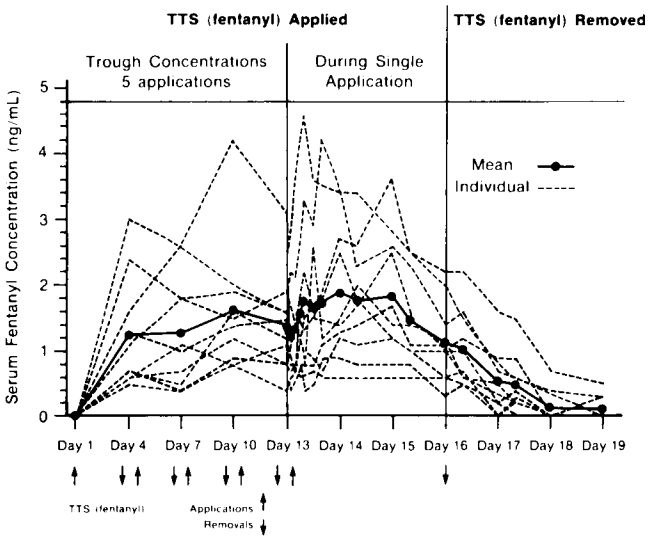

Fig. 1. Individual and mean (SE) serum fentanyl concentration-time profiles measured in ten patients during five consecutive applications of the transdermal system.

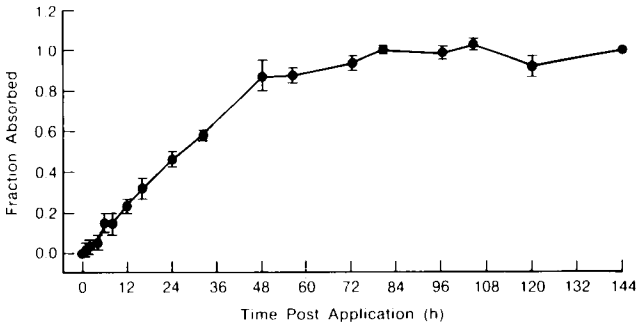

Fig. 2. Mean (SE) fractional absorption of fentanyl following the fifth application of the transdermal system in eight patients.

attributable to the use of the transdermal system. Side effects that were rated as "probably related" to the study drug were lethargy in eight patients, nausea in three, confusion or mood change in two, hypotension in two, anorexia in two, dizziness in two, and constipation in one. Four patients developed mild erythema at the application site of the transdermal system.

Following completion of the study, six patients (five women, one man) continued to receive the transdermal fentanyl system. Their median age was 64 yr (range 50–67 yr). The median time of this extended treatment phase was 30 days (range 6–122 days). The fentanyl dose was adjusted in some patients according to analgesic requirements; all patients received a total dose of either 100 μg/h or 200 μg/h. Four patients subsequently discontinued treatment due to progressive cancer; one discontinued after experiencing hair loss that the investigators did not attribute to the fentanyl. One became asymptomatic and did not require analgesics. During the extended treatment phases, the system was generally well tolerated. Side effects that were "probably related" to the study drug included constipation in one patient, lethargy and dizziness in one, and lethargy and abdominal distention in one.

Discussion

Although the skin acts as an effective barrier to the absorption of most drugs, some drugs possess the physicochemical characteristics and potency necessary for transdermal delivery.[13] Transdermal formulations

Table 2. Pharmacokinetic Parameter Estimates for the Serum Concentration Profile of Fentanyl Measured during the Fifth Application of the Transdermal System

Subject No.	C_{max} (ng/ml)	C_{min} (ng/ml)	C_{avg} (ng/ml)	Apparent Halflife (h)	Apparent Rate Constant (h^{-1})	AUC_{0-72} ($ng \cdot h^{-1} \cdot ml^{-1}$)	AUC_{inf} ($ng \cdot h^{-1} \cdot ml^{-1}$)
1	4.6	2.2	3.09	25.0	0.028	222.3	221.1
2	3.6	1.1	2.43	20.9	0.033	174.7	189.8
3	4.2	1.4	2.61	16.2	0.043	187.9	199.3
4	2.6	0.7	1.48	12.8	0.054	106.2	94.3
5	0.9	0.3	0.71	31.4	0.022	50.2	62.1
6	1.9	0.6	1.04	28.2	0.025	75.0	21.9
7	1.1	0.6	0.59	21.7	0.032	42.4	24.0
8	2.5	1.0	1.63	38.1	0.018	117.5	111.9
9	1.7	0.5	1.20	15.4	0.045	86.2	91.9
10	2.5	0.7	1.50	9.7	0.072	107.9	117.2
Mean	2.6	0.91	1.62	21.9	0.037	116.9	113.2
SD	1.3	0.55	0.83	8.9	0.017	59.9	70.3

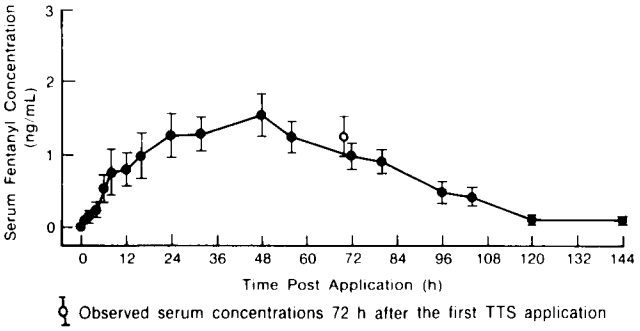

Fig. 3. Mean (SE) serum fentanyl concentration-time profile (closed circles) for a first application of the transdermal system predicted from the profiles measured during the fifth application in ten patients. The actual mean (SE) serum trough concentration measured 72 h after the first application is indicated by the single open circle.

for nitroglycerin,[14] estradiol,[15] scopolamine,[16,17] and clonidine[18] are in clinical use, and experience with these drugs has established both the feasibility and acceptability of long-term transdermal therapy. Pharmacokinetic studies indicate that rate-controlled transdermal systems maintain serum drug concentration for a prolonged period following application to the skin.[14,17,18] These kinetics allow less frequent dosing and can produce smaller, and more gradual, fluctuations in serum drug concentration than repeated-bolus dosing by other routes.

The development of transdermal systems for opioid drugs may provide a useful route of administration for some patients with chronic pain who require long-term parenteral administration of an analgesic drug[19]; their utility is most likely to be apparent in the population with chronic cancer pain. The approach may expand the clinical options for some opioids, such as fentanyl, that have not been used previously for chronic pain due to a short duration of effect following a dose. Clinical experience with these systems is needed to evaluate the possibility of additional advantages (such as improved compliance with treatment or acceptability of analgesia) and potential disadvantages (such as inflexibility of dosing and the slow onset of effects when the system is first applied or the dose increased).

With repeated application of the transdermal system at 72-h intervals, steady-state serum fentanyl concentrations are approximated by the time of the second dose. This is suggested by the relatively small differences among the trough concentrations measured prior to the second through fifth doses. Evidence that steady state has been reached by the fifth dose is provided by the similarity between the AUC_{0-72} and the AUC_{inf} calculated from the serum concentrations measured during this dose.

As steady state is approached, there appears to be no significant alteration in drug absorption or metabolism. This conclusion is supported by the stability of the dose absorbed over repeated administrations and the similarity between the results predicted from a simulation of single dose pharmacokinetics and an observed serum concentration following the first dose. At steady state, almost 50% of the total dose delivered during 72 h is absorbed within the first 24 h and more than 80% is absorbed within 48 h. As would be expected from these absorption kinetics, the maximum concentration is attained within the first day of application (fig. 1). Following removal of the transdermal system, the mean apparent half-life is approximately a day. This is longer than the elimination half-life of fentanyl observed following intravenous administration.[10] A slower decline in serum drug concentration following the discontinuation of transdermal administration is due to continued absorption of fentanyl from the skin.

These data are similar to previous pharmacokinetic observations. A study[6] of the TTS(fentanyl)-100 system indicated that a relatively stable serum concentration was achieved by 15–24 h after a single application; the mean serum concentration at this time was 2.15 ng/ml, and the apparent half-life following removal of the system was approximately 21 h. Other studies have similarly observed that serum fentanyl concentrations stabilize during the latter part of the first day of use,[10] and an apparent half-life of 16–25 h has been recorded in numerous studies.[8–10] A recent study[10] reported that the average (SD) bioavailability of fentanyl delivered via the TTS(fentanyl)-100 system was 0.92 (0.33).

Like previous investigations, the current study reveals large variability in the distributions of each pharmacokinetic parameter estimate. Variability in serum fentanyl concentrations reflects some combination of individual differences in serum fentanyl elimination kinetics, variation in the transdermal absorption kinetics, and variability in doses delivered by transdermal systems. Of these, individual differences appear to be the major factor. Previous studies have demonstrated that serum fentanyl kinetics are characterized by large interindividual variability,[10,20–22] similar to the pharmacokinetics of other opioid drugs.[23–29] Although dose to dose variability in the transdermal system has been suggested by one study,[9] and is likely given the variation in the dose absorbed, the present study suggests that

this, too, contributes relatively little to the overall variability in the data. The finding that intrasubject variation in trough serum concentrations is smaller than intersubject variation also supports the conclusion that individual differences account for most of the variability.

In the clinical use of the transdermal system, interindividual variability in pharmacokinetics is unlikely to be a substantial problem if clinical practice incorporates both a conservative starting dose and dose titration based on observed effects. Intraindividual variability could alter a patient's response to a dose over time, and potentially presents a greater clinical problem. The present data, and limited information from chronic dosing surveys,[4,5] suggest that intraindividual variability is small enough to be clinically irrelevant, but additional experience with the transdermal system will be needed to confirm this conclusion.

The transdermal fentanyl system was well tolerated in the opioid-tolerant patients who participated in the study. Neither the expected exacerbation of opioid-related side effects nor the only adverse effect attributable to the system's presence on the skin (mild erythema at the application site) was severe enough to cause any patient to discontinue the study.

These data have other implications for the clinical use of the TTS(fentanyl) system. Dosing at 3-day intervals will yield serum concentrations that approximate steady-state levels during the first dose. Pharmacokinetics are stable over at least five repeated applications. With each dose, serum concentration generally rises to a peak level between 24 and 48 h, after which a gradual decline occurs. The efficacy of the dose, therefore, should become apparent within a day after dosing is initiated or increased. Toxicity from each system, if it is to occur, is also most likely appear during the first day after application. Following removal of the system, fentanyl concentrations decline with an apparent half-life that may extend for a day or more. Effects should not be anticipated to diminish for many hours after the system is removed. Patients who develop serious adverse effects must be monitored for a period commensurate with this slow decline in the serum concentration of the drug.

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