Reproducible Fentanyl Doses Delivered Intermittently at Different Time Intervals from an Electrotransport System

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Abstract □ The electrotransport transdermal fentanyl system (ET [fentanyl]), uses a small electrical current to enhance delivery of fentanyl to systemic circulation. Intermittent doses can be administered by periodic application of the current. The purpose of this study was to compare the effects of the frequency of intermittent drug delivery by ET (fentanyl) and compare the drug delivery to systemic circulation by ET (fentanyl) with intravenous administration. The topical safety was also determined for the ET (fentanyl) system. Nine adult male volunteers completed this three-treatment, randomized, 24-h, crossover study. ET (fentanyl) treatments with 200 μA direct current applied for 30 min at frequent (hourly) or infrequent (4-hourly) intervals over a 24-h period were compared. Also, the drug delivery to systemic circulation from ET (fentanyl) was compared with intravenous fentanyl 75 μg infused over 30 min every 4 h over a 24-hour period. The mean serum fentanyl concentration achieved with the hourly ET (fentanyl) regimen was higher than that for the 4-hourly ET (fentanyl) regimen as expected from the higher frequency of drug doses. The amount of fentanyl delivered estimated per dose from the ET (fentanyl) system using the iv fentanyl treatment as the reference was similar for the two ET regimens throughout the dosing period. This indicates consistent drug delivery regardless of the frequency of ET dosing. The majority of subjects reported either no, or barely perceptible, erythema 24 h after removal of the system.

Introduction

Fentanyl is a short-acting synthetic opioid analgesic. When administered by a passive transdermal system (Duragesic [U.S.]/Durogesic [outside U.S.]), fentanyl is effective for the treatment of moderate to severe chronic pain.[3] Compared to intravenous or oral routes for delivering analgesia, the passive transdermal system has the advantages of being a noninvasive, nonoral route that maintains adequate serum concentrations for the duration of application (for Duragesic, a patch has to be applied every 72 h).[4,5] The fentanyl passive transdermal system has proven effective for control of chronic pain; however, it is not suitable for managing postoperative pain and other acute or intermittent pain conditions.[4]

Analgesic delivery systems that are controlled by the patient (patient-controlled analgesia or PCA) provide better pain control than standard modes of delivery because they allow continuous patient access to pain medication within predetermined limits.[1] Such PCA systems are both efficacious and well accepted. The PCA systems are fully computerized portable syringe pumps with a reservoir for the drug solution. The pump delivers the drug into an intravenous access site on the patient via microbore tubing.

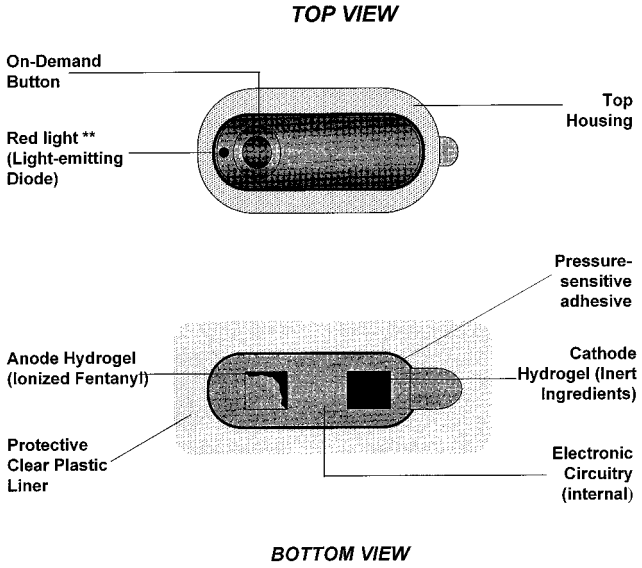

Figure 1—Schematic diagram of ET (fentanyl) system (**indicates when a dose is being delivered, as well as the approximate number of doses the patient has received since application of the particular system).

These pumps have visual displays providing information on patients drug consumption minute by minute. From the PCA systems, the drug can be either administered as a bolus injection, continuous infusion over a period of time, or continuous background infusion plus bolus whenever needed.[2] The economic advantages of PCA include lower cost due to the decreased need for medical intervention and, potentially, earlier release from the medical facility. Unfortunately, PCA equipment is costly, cumbersome, and invasive, and it requires maintenance and sterilization.

An electrotransport (ET) transdermal system for fentanyl has been developed which combines the advantages offered by PCA and the passive transdermal system. The ET system enhances the delivery of drug by means of an electrical current. Application of an electrical field facilitates the transport of charged compounds across the skin. A number of comprehensive reviews on the subject of electrotransport or iontophoresis have been written.[6–8] The pathways of molecular transport through the skin during iontophoresis have also been extensively studied.[19,20] The commercial ET system is a lightweight, self-contained system, worn on the patient's upper outer arm or chest. The system contains internal electronic circuitry, a battery, anode and cathode hydrogels, and an external button to activate delivery of fentanyl. The system is backed with a pressure-sensitive adhesive which allows it to stick to the skin (Figure 1). As with PCA, the drug delivery rate can be set by adjusting the current; as the current is increased, the rate of drug delivery is increased.[9] Intermittent doses

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can be administered by switching the current on for a predetermined period of time (dosing period). This system can, therefore, effectively manage acute or intermittent pain conditions.

The purpose of this randomized crossover study was to compare fentanyl delivery to systemic circulation from frequent intermittent doses administered hourly to infrequent doses administered every 4-hours by an ET (fentanyl) system. An additional objective was to compare serum concentrations achieved from ET (fentanyl) treatments with the reference intravenous (iv) treatment, and estimate the fentanyl dose delivered to systemic circulation from ET (fentanyl) treatments using this reference treatment. The study also evaluated the topical safety of fentanyl delivered by ET (fentanyl) system.

Materials and Methods

The study enrolled 10 healthy adult male volunteers (all Caucasian, aged 20−37 years [mean 27.3, SD 4.8]) to ensure that nine subjects would complete the study. Subjects were within 10% of ideal weight, nonsmokers with no history of drug or alcohol abuse, and they had abstained from recreational drug use within the past 30 days. Subjects also agreed to abstain from alcohol from 48 h before the study started until the end of the study. Exclusion criteria included active skin disease that precluded application of the system; a history of CO_2 retention, asthma or other lung disease; other clinically significant medical problems or organ abnormalities; hemoglobin <13 g/dL; or a history of allergic reaction to fentanyl, other opioids, or naltrexone. The subjects were also screened for physical dependence on opioids by Narcan (Naloxone hydrochloride: Endo Pharmaceuticals, Wilmington, DE) challenge test.[10] The protocol and consent form were reviewed and approved by the Institutional Review Board of Inveresk Clinical Research Ltd. (Edinburgh, Scotland) before the study started.

This was a randomized, open-label, three-treatment, three-period, crossover study. Each subject received three 24-h fentanyl treatments separated by 6-day washout periods. The ET (fentanyl) system (E-TRANS [fentanyl], ALZA Corporation, Palo Alto, CA), using direct current at 200 μA over a 30-min interval, was compared with 75 μg of fentanyl iv delivered over the same interval. The prototype ET (fentanyl) system used in this study consisted of a custom-built current source (Medtronic Model 6443) attached to the wrist and connected by a cable to a patchlike drug unit. The drug unit was composed of two poly(vinyl alcohol) hydrogels: one contacting a silver anode (2 cm^2) and containing fentanyl hydrochloride (10 mg) with polymeric buffer, the other contacting a silver chloride cathode (6.5 cm^2) and containing a biocompatible buffered electrolyte. The hydrogels and electrodes were housed in a medical-grade polyethylene foam with a peripheral acrylic adhesive. The ET (fentanyl) application site (upper arm) was wiped with an alcohol swab as is normally done for cleansing purposes and then either wiped dry or allowed to air-dry. The drug unit was placed on the upper arm after the peel-off protective liner was removed from the adhesive layer.

Fentanyl was delivered for the first 30 min of each hour (regimen A) or for the first 30 min of every fourth hour (regimen B). Fentanyl solution (50 μg/mL) was administered intravenously by a portable, battery-operated, syringe driver pump (Model MS2000; Graseby Medical Ltd., Watford, Hertfordshire, UK) at a rate of 1.5 mL (75 μg) over the first 30 min of every fourth hour (total dose over 24 h, 525 μg; regimen C). To minimize the opioid effects of fentanyl, five doses of naltrexone 50 mg were administered at 12-h intervals, starting 14 h before the first fentanyl dose.

Blood samples were drawn immediately before the initial fentanyl administration and periodically throughout the treatment: 10, 20, 30, 45, 60 min post 0, 12, and 24 h dosing, and also at 25, 26, 28, 32, 36 and 48 h posttreatment initiation. Serum samples were assayed for fentanyl at Janssen Research Foundation (Beerse, Belgium) using a radioimmunoassay method with a quantification limit of 0.1 ng/mL.[11]

Pharmacokinetic Analysis—The average maximum serum fentanyl concentration (C_{max} in ng/mL) and corresponding time (T_{max} in hours) observed during the entire 24-h treatment regimen were calculated. Serum fentanyl elimination rate constants (k) were estimated by linear regression of log-transformed (natural log) serum fentanyl concentrations during the terminal log-linear phase of the data after system removal. Apparent half-life ($t_{1/2}$) values were calculated as 0.693/k.

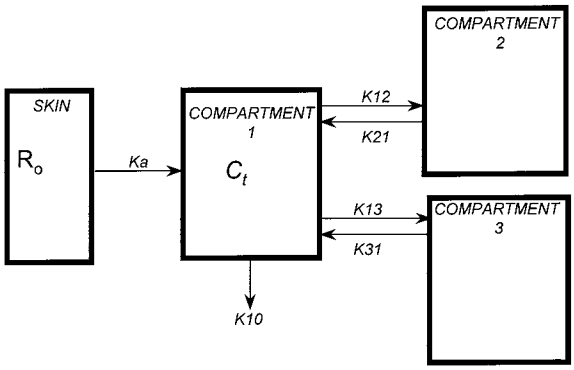

Figure 2—Three-compartment model for fentanyl administered by ET (fentanyl) system and by intravenous infusion (C_p = serum fentanyl concentrations).

For all three regimens, the area under the fentanyl concentration−time curve [$AUC_{(n-n+1)}$] was calculated by the linear trapezoidal method for doses administered during hours 0−1, 12−13, and 24−25, when frequent blood sampling was performed. For the two 4 h regimens (ET and iv), the $AUC_{(24-28)}$ (AUC for one dosing interval) was also estimated.

Statistical Analysis—An analysis of variance (ANOVA) was used to (i) compare $AUC_{(0-1)}$ among the three treatments and (ii) compare steady-state AUC over one dosing interval after the last dose ($AUC_{(24-25)}$ for the hourly regimen and $AUC_{(24-28)}$ for the 4 hly regimen) among the three treatments.

Compartmental Modeling—A three-compartment open distribution model was used to describe the observed fentanyl concentration−time profile after iv infusion. Equation 1 defines the three-compartment disposition model for administration of a single dose by iv infusion.[12] For fentanyl administration by the ET system, absorption was described by first-order kinetics (Figure 2).

$$C(_{t'}) = \frac{R_{iv}\,(1 - e^{\alpha\theta})(k_{21} - \alpha)(k_{31} - \alpha)e^{-\alpha t'}}{-V_1\alpha(\beta - \alpha)(\gamma - \alpha)} + \frac{R_{iv}\,(1 - e^{\beta\theta})(k_{21} - \beta)(k_{31} - \beta)e^{-\beta t'}}{-V_1\beta(\alpha - \beta)(\gamma - \beta)} + \frac{R_{iv}(1 - e^{\gamma\theta})(k_{21} - \gamma)(k_{31} - \gamma)e^{-\gamma t'}}{-V_1\gamma(\beta - \gamma)(\alpha - \gamma)} \quad (1)$$

Equation 2 describes the three-compartment disposition model for a single intermittent dose from an ET (fentanyl) system.[12] The absorption rate constant in this equation defines absorption due to both electrotransport and passive diffusion if any from the ET (fentanyl) system. In a previous study[13] the passive delivery of fentanyl from an ET (fentanyl) system was shown to be negligible. Four models for the ET (fentanyl) treatments were evaluated as described below. Model selection was based on residual sum of squares (RSS) and the Akaike information criterion (AIC).[14] A model with lower RSS and AIC values is preferred.

$$C_{(t')} = \frac{R_t k_a(1 - e^{\alpha\theta})(k_{21} - \alpha)(k_{31} - \alpha)e^{-\alpha t'}}{-V_1\alpha(\beta - \alpha)(\gamma - \alpha)(k_a - \alpha)} + \frac{R_t k_a(1 - e^{\beta\theta})(k_{21} - \beta)(k_{31} - \beta)e^{-\beta t'}}{-V_1\beta(\alpha - \beta)(\gamma - \beta)(k_a - \beta)} + \frac{R_t k_a(1 - e^{\gamma\theta})(k_{21} - \gamma)(k_{31} - \gamma)e^{-\gamma t'}}{-V_1\gamma(\beta - \gamma)(\alpha - \gamma)(k_a - \gamma)} + \frac{R_t k_a(1 - e^{k_a\theta})(k_{21} - k_a)(k_{31} - k_a)e^{-k_a t'}}{-V_1 k_a(\alpha - k_a)(\beta - k_a)(\gamma - k_a)} \quad (2)$$

where

t = Time since initiation of the treatment

$C_{(t')}$ = Concentration at time t′

t' = Time since initiation of the last input

α = First disposition rate constant

β = Second disposition rate constant

γ = Third disposition rate constant

k_{21} = Rate constant for transfer from second compartment to the central compartment

k_{31} = Rate constant for transfer from third compartment to the central compartment

V_1 = Volume of distribution of the central compartment

k_a = Transdermal absorption rate constant

R_{iv} = Rate of intravenous infusion (150 μg/h over 0.5 h)

R_o = Rate of fentanyl input after ET system dose at initiation and throughout for model 1

R_t = Rate of fentanyl input after ET system dose at time t:

= R_o (from 0−12 h); R_1 (from 12−24 h); R_2 (from 24−25 h) [stepwise increase in rate of fentanyl input such that $R_o < R_1 < R_2$; model 2

= $R_o + st$ [linear increase in rate of fentanyl input; model 3]

= $R_o (2\text{-}e^{-st})$ [exponential increase in rate of fentanyl input; model 4]

s = Slope constant to account for increase in the input rate

CL = Clearance = $V_1\alpha\beta\gamma/k_{21}k_{31}$

θ = t' when $t' \leq 0.5$ or 0.5 when $t' > 0.5$

The profiles for multiple dose applications were then obtained by superposition of the profile associated with each administration given before t:

$$C_{(t)} = \sum_{j=1}^{M} C^{j}_{(t-(j-1)\tau)} \qquad (3)$$

where

$C_{(t)}$ = Concentration at time t

j = jth administration before t

M = Total number of administrations

τ = Dosing interval

These equations were simultaneously fitted to the all plasma concentration from each subject following all three treatments. Models were fitted to only those serum fentanyl concentration values above the quantification limit (concentrations below limit of quantification were set to missing). Pharmacokinetic disposition parameters and absorption parameters (both amount and absorption rate constants) were estimated by nonlinear regression, using the PROC NLIN procedure in SAS 6.04, with the "power model" weighting function.[15]

Safety Analysis—Safety was evaluated by analysis of pre- and poststudy blood chemistry, hematology, and urinalysis data, as well as physical examination results and electrocardiograms. During each 24-h administration period, and for 24 h after the end of each administration period, vital signs (heart rate, blood pressure, and respiratory rate) were recorded periodically. At 1, 6, and 24 h after system removal, the skin occluded by the system was evaluated visually, and any evidence of local reaction was scored as follows:

Erythema: 0 = none; 1 = barely perceptible redness; 2 = definite redness; 3 = beet redness.

Edema: Extent of erythema, papules, pustules: 0 = none; 1 = <50% occluded area; 2 = >50% occluded area.

Itching: 0 = none; 1 = mild; 2 = moderate; 3 = severe.

Results and Discussion

Ten healthy Caucasian males, aged 20−37 years (mean 27.3, SD 4.8), entered the study, and nine subjects completed. One subject discontinued study participation for a non-drug-related (personal) reason after completing the first regimen (fentanyl delivered by the ET system for 30 min/h). Data from the nine subjects who completed the study are included in the pharmacokinetic analysis, and data from all 10 subjects enrolled are included in the safety analysis. None of the subjects showed any signs or symptoms of withdrawal after administration of the Narcan challenge.

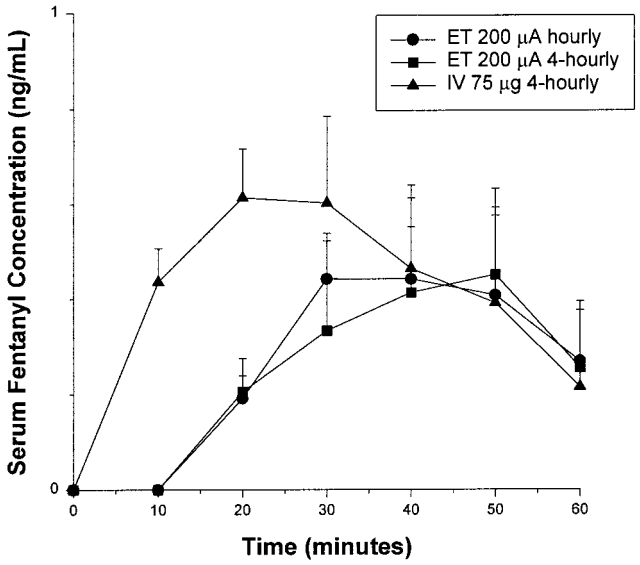

Figure 3—Mean (±SD) serum fentanyl concentrations for the first hour of the three 24-hour fentanyl regimens (n = 9). (Note: Concentrations below limit of quantification are set to zero value).

For three subjects, the duration of fentanyl administration in regimen A (30 min/h) deviated from the approved protocol. One subject received fentanyl for 1 h instead of 30 min, from hour 14 to hour 15 (half-hourly administration was restarted at hour 16). Two subjects received fentanyl for only 20 min during hour 5. The actual duration of drug administration was accounted for in the compartmental analysis.

Fentanyl Pharmacokinetics—Mean serum fentanyl concentrations increased after the first set of intermittent doses at hour 0 for both ET (fentanyl) regimens. However, the rate of increase with the ET (fentanyl) regimens was slower than that of the iv regimen (Figure 3) and serum fentanyl concentration 10 min after the dose was not detectable. Also, the mean serum fentanyl concentration declined rapidly upon termination of the iv infusion at hour 0.5, but when the ET (fentanyl) dosing interval ended, serum fentanyl concentrations did not decline for approximately 10 min (Figure 3). Similar observations were made following intermittent dosing at hours 12 and 24. These observations suggest that the barrier effect of the skin moderates both the rise and fall of serum fentanyl concentrations with ET (fentanyl) administration. Serum concentration profiles for the three regimens are shown in Figure 4. Following the hour 24 dose, the mean serum fentanyl concentration for the ET (fentanyl) hourly regimen was approximately 4-fold higher than that for the ET (fentanyl) 4-hourly regimen, which, in turn, was about twice as high as that for the iv 4-hourly regimen.

The mean fentanyl pharmacokinetic parameters are listed in Table 1. The mean C_{max} value for the ET (fentanyl) hourly regimen (2.6 ng/mL) was higher than those for the ET (fentanyl) 4-hourly or iv 4-hourly regimens (1.3 and 0.9 ng/mL, respectively). The T_{max} values for most subjects were between 24 and 25 h, with median values of 25 h after ET (fentanyl) administration and 24 h after iv administration.

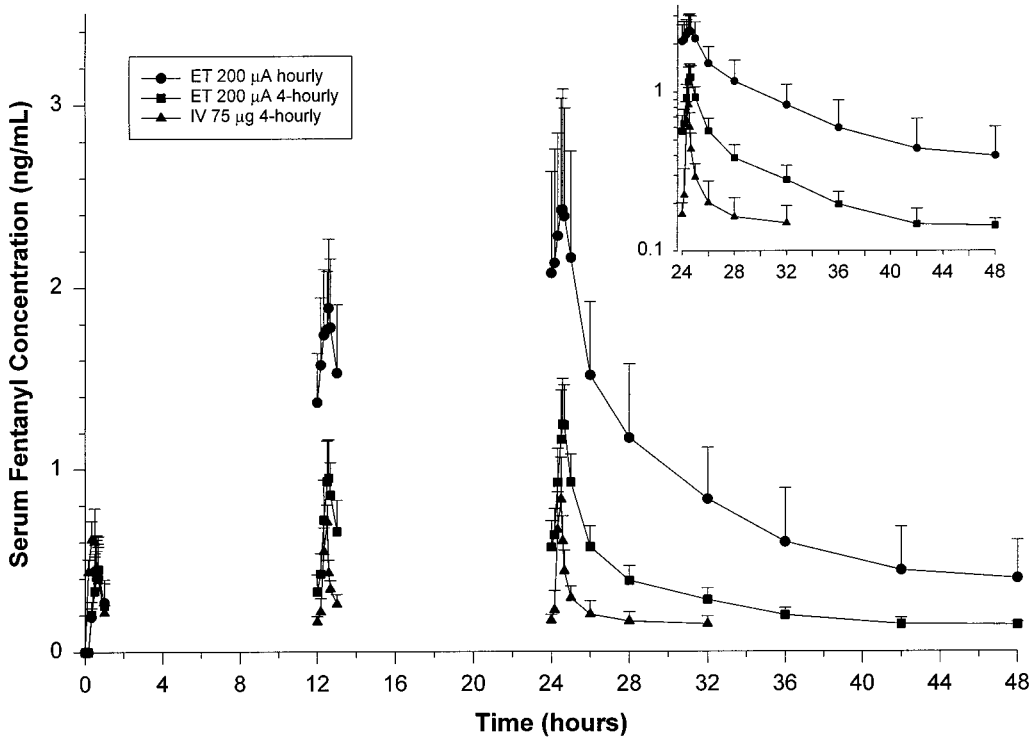

Figure 4—Mean (±SD) serum fentanyl concentrations for the three 24-hour fentanyl regimens ($n = 9$). Serum fentanyl concentrations were measured during hours 0–1, 12–13, and 24–25.

Table 1—Mean (± SD) Fentanyl Pharmacokinetic Parameters in Nine Healthy Volunteers[a]

		regimen		
parameter	units	A ET (fentanyl) hourly	B ET (fentanyl) 4-hourly	C iv 4-hourly
C_{max}	ng/mL	2.6 ± 0.7	1.3 ± 0.3	0.9 ± 0.2
T_{max}[b]	h	23.3 ± 4.0	23.3 ± 4.0	15.2 ± 11.6
K	h^{-1}	0.053 ± 0.029	0.083 ± 0.031	0.308 ± 0.257
$t_{1/2}$	h	22.0 ± 21.0	10.0 ± 5.6	3.4 ± 1.7
$AUC_{(0-1)}$	ng·h/mL	0.25 ± 0.11*	0.24 ± 0.13*	0.39 ± 0.08**
$AUC_{(12-13)}$	ng·h/mL	1.67 ± 0.35	0.75 ± 0.17	0.36 ± 0.04
$AUC_{(24-25)}$ for hourly regimen $AUC_{(24-28)}$ for 4-hourly regimen	ng·h/mL	2.23 ± 0.59*	2.66 ± 0.45*	1.00 ± 0.33**

[a] Abbreviations: C_{max}, peak serum concentration; T_{max}, time to peak concentration; k, apparent elimination rate constant; $t_{1/2}$, apparent half-life; AUC, area under the serum concentration–time curve. [b] The mean value for intravenous administration was skewed downward by three outlying values of <1 h. Median values for the three treatments were 25 h (regimens A and B) and 24 h (regimen C). Note: C_{max} and T_{max} are over the entire treatment period. *Parameters with the same number of asterisks are not significantly different ($p<0.05$).

A polyexponential decline of serum fentanyl concentrations occurred after the last dose in all three regimens (Figure 4). The mean apparent half-life values varied widely among the three regimens; half-lives were longer for the two ET (fentanyl) regimens (regimen A = 22.0 h; regimen B = 10.0 h) than for the iv regimen (regimen C = 3.4 h). Due to the assay sensitivity (0.1 ng/mL), the serum concentrations for all subjects could be quantified to hour 26 for the iv treatment, to hour 32 for the ET (fentanyl) 4-hourly regimen, and to a much longer duration of up to hour 48 for the ET (fentanyl) hourly regimen. This suggests that only the distribution phase, rather than the terminal elimination phase, was observed after the 4-hourly ET (fentanyl) and iv regimens. This probably was the reason for apparent half-life values for these two regimens to be shorter than it would be if the terminal elimination phase could have been quantified. This explanation is further supported by the previously reported terminal elimination half-life of 8 h following iv fentanyl adminsitration.[16] Alternatively, the long mean apparent half-life of the hourly ET (fentanyl) regimen (which was due mainly to two subjects with long apparent half-life values of 49.5 and 65.8 h) may indicate some contribution of the skin to the apparent terminal phase of the ET (fentanyl) regimens. However, if the long apparent terminal half-life observed after ET (fentanyl) administration was the electrotransport absorption half-life value, then the increase in serum fentanyl concentrations after a supplemental fentanyl dose would have been much more delayed than that observed. It appears that for ET fentanyl the depot or the reservoir effect is not as pronounced as seen with the transdermal system. With passive fentanyl transdermal system (Duragesic), the terminal half-life is severalfolds higher than that observed with intravenous fentanyl.[17] In the passive transdermal system, ethanol is incorporated to enhance drug solubility in the system and to enhance drug flux through the skin. Thus, fentanyl flux depends on the ethanol concentration being delivered. Ethanol flux is about 500 times greater than fentanyl flux.[18] After the system is removed, the ethanol in the skin is absorbed into systemic circulation much faster than fentanyl. This causes the rate of fentanyl appearing in systemic circulation to decrease

Table 2—Estimated Pharmacokinetic Parameters by Fitting the Three-Compartment Model to Serum Fentanyl Concentration Following Intravenous Administration and ET (fentanyl) Application (model 4) in Nine Healthy Volunteers[a]

subject no.	α, h^{-1}	β, h^{-1}	γ, h^{-1}	k_{21}, h^{-1}	k_{31}, h^{-1}	V_1, L	k_a, h^{-1}	S_a, h^{-1}	S_b, h^{-1}	ET rate (μg/h)	k_{10}, h^{-1}	k_{13}, h^{-1}	k_{12}, h^{-1}	CL, L/h
101	3.90	0.057	0.162	0.602	0.095	68.5	5.13	0.027	0.074	137.9	0.625	0.205	2.59	42.8
102	3.54	0.051	0.322	0.633	0.103	68.0	5.45	0.210	0.120	118.4	0.900	0.714	1.57	61.2
104	6.62	0.630	0.061	1.383	0.118	52.4	0.90	0.033	0.246	177.2	1.572	1.259	2.98	82.5
105	6.02	0.367	0.045	1.104	0.125	55.0	2.80	0.076	0.068	178.5	0.730	0.927	3.54	40.1
106	6.43	0.240	0.068	0.723	0.105	48.9	2.57	0.025	0.041	261.8	1.387	0.487	4.04	67.8
107	5.57	0.363	0.027	1.237	0.044	54.9	5.72	0.076	0.098	156.7	1.016	0.557	3.10	55.8
108	6.44	0.254	0.066	0.867	0.094	48.3	2.78	0.028	0.148	202.3	1.326	0.388	4.08	64.0
109	2.64	0.567	0.065	1.129	0.145	88.9	6.43	0.089	0.165	165.3	0.598	0.590	0.81	53.2
110	6.90	0.433	0.097	1.418	0.209	48.6	4.69	0.455	0.089	117.2	0.978	0.666	4.16	47.5
mean	5.34	0.329	0.102	1.012	0.115	59.3	4.05	0.113	0.117	168.4	1.015	0.644	2.99	57.2
SD	1.56	0.202	0.091	0.315	0.045	13.6	1.85	0.141	0.625	45.1	0.348	0.308	1.17	13.3
SE	0.52	0.067	0.030	0.105	0.015	4.52	0.62	0.047	0.021	15.0	0.116	0.103	0.39	4.44
Gmean	5.09	0.249	0.079	0.964	0.107	58.1	3.54	0.068	0.103	163.4	0.962	0.577	2.69	55.9
max.	6.90	0.630	0.322	1.418	0.209	88.9	6.43	0.455	0.246	261.8	1.572	1.259	4.16	82.5
min	2.64	0.051	0.027	0.602	0.044	48.3	0.90	0.025	0.041	117.2	0.598	0.205	0.81	40.1

[a] α = First disposition rate constant. β = Second disposition rate constant. γ = Third disposition rate constant compartment. k_{21} = Rate constant for transfer from the second compartment to the central compartment. k_{31} = Rate constant for transfer from the third compartment to the central compartment. k_{10} = Elimination rate constant from the central compartment to out. k_{13} = Elimination rate constant from the central compartment to the third. k_{12} = Elimination rate constant from the central compartment to the second compartment. k_a = Transdermal absorption rate constant. CL = Clearance = $(V_1\alpha\beta\gamma/k_{21}k_{31})$. V_1 = Volume of distribution of the central compartment. S_a = Slope constant to account for increase in the input rate for treatment A. S_b = Slope constant to account for increase in the input rate for treatment B.

(forms a reservoir in the skin) and the terminal half-life is longer than that observed with intravenous administration.[18]

The $AUC_{(0-1)}$ values for the ET (fentanyl) regimens were similar (0.25 and 0.24 ng·h/mL) and were significantly lower ($p < 0.05$), approximately 60% of the value for the iv regimen (0.39 ng·h/mL). However, a direct comparison of the $AUC_{(0-1)}$ values may not be an exact reflection of the dose delivered to the systemic circulation because the profiles for the ET (fentanyl) regimens are shifted to the right of the iv regimen profile, and the concentrations at hour 1 for the ET (fentanyl) regimens are approximately 10% to 15% higher than that for the iv regimen. In contrast, the steady-state AUC after the last dose − mean $AUC_{(24-25)}$ for the ET (fentanyl) hourly regimen and $AUC_{(24-28)}$ for the ET (fentanyl) 4-hourly regimen were significantly more (2-fold) than that of $AUC_{(24-28)}$ for the iv administration. This is discussed further in the Compartmental Modeling section below.

Compartmental Modeling—Compartmental modeling was used to determine the exact amount of fentanyl delivered by the ET (fentanyl) treatments using iv regimen as the reference. Since the serum fentanyl concentrations declined polyexponentially (Figure 4), a model with first-order absorption and triexponential disposition was fitted to the data for the ET (fentanyl) regimens, and a triexponential disposition model was fitted to the data for the iv regimen (eq 1). This model (model 1) was able describe the iv data well. However, for the ET (fentanyl) treatments, with this model (model 1), the observations near hour 24 were underestimated and those near hour 0 were overestimated, suggesting that the amount of fentanyl delivered to the systemic circulation with the ET system increased with time. Three other models (allowing different amounts of fentanyl input at each dose interval) which were modifications of model 1 were investigated. Model 2 allowed stepwise increase in the input rate in eq 2; results from this model showed that the mean rate of input at hour 24 was nearly twice that for input at hour 0. However, since the input rate change is probably a gradual and continuous change rather than a step function, the model was further modified so that the input increased linearly (model 3) or exponentially (model 4) with time (eq 2). For most subjects, the RSS and AIC values with model 4 were less than model

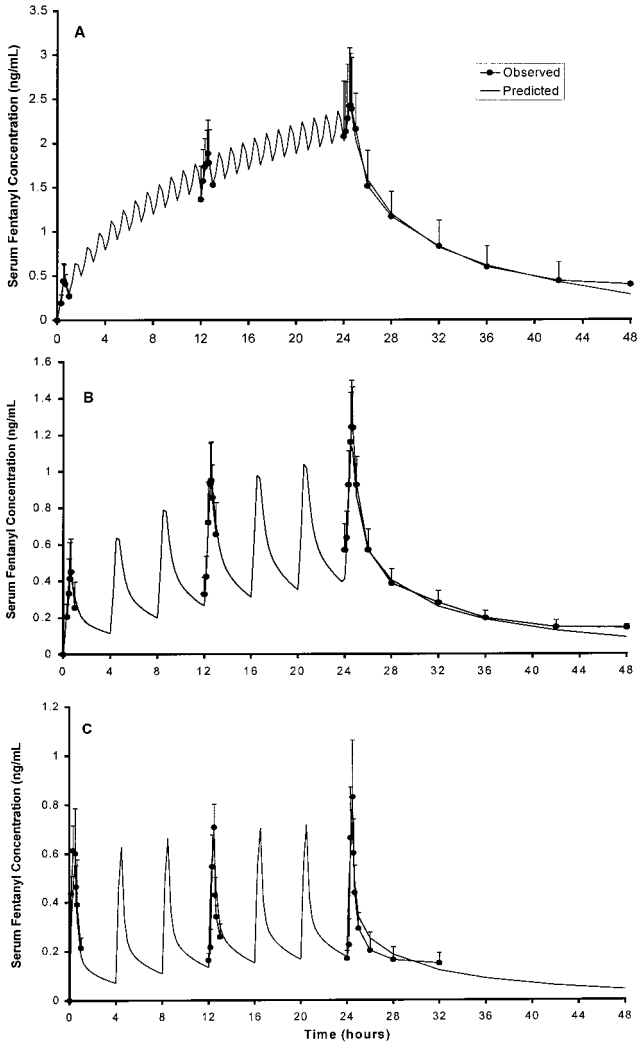

Figure 5—Model predicted and observed (mean ± SD) serum fentanyl concentrations for the three 24-hour fentanyl regimens (n = 9). A = ET (fentanyl) hourly regimen; B = ET (fentanyl) 4-hourly regimen; C = iv (fentanyl) 4-hourly regimen.

Table 3—Summary of Skin Site Reactions 1, 6, and 24 Hours after System Removal

	number of subjects					
	A ET (fentanyl) hourly ($n = 10$)			B ET (fentanyl) 4-hourly ($n = 9$)		
	1 h	6 h	24 h	1 h	6 h	24 h
erythema						
None	0	0	1	0	0	0
Barely Perceptible Redness	2	7	4	1	7	6
Definite Redness	6	2	4	8	2	3
Beet Redness	2	1	1	0	0	0
edema						
None	9	10	10	8	8	8
<50% Occluded Area	1	0	0	1	1	1
<50% Occluded Area	0	0	0	0	0	0
papules						
None	10	10	10	9	8	8
<50% Occluded Area	0	0	0	0	1	1
<50% Occluded Area	0	0	0	0	0	0
itching						
None	10	10	9	8	6	7
Mild	0	0	1	1	3	1
Moderate	0	0	0	0	0	1
Severe	0	0	0	0	0	0

3. Figure 5 shows good agreement between the model predicted concentration and the observed concentration. The rate constants for model 4 are shown in Table 2. Using model 4 parameters, the estimated amounts of fentanyl delivered to the systemic circulation at hours 0, 12, and 24 for the ET (fentanyl) hourly regimen and the ET (fentanyl) 4-hourly regimen were determined ($R_t = R_o[2 - e^{-st}]$; eq 2). The estimated amount of fentanyl delivered in 30 min at 0, 12, and 24 h were 84, 126, and 142 μg, respectively, for the hourly treatment, and 84, 142, and 157 μg, respectively, for the 4-hourly treatment. The increase in the amount of fentanyl delivered at the 24 h time point may be due to skin (depot effect, permeability changes, etc.) equilibrating with the delivery system (current, occlusion, etc). However, any conclusion regarding a time-dependent fentanyl input rate phenomenon should be considered tentative because it is highly dependent on the plasma concentration data from the first intermittent delivery period; these concentrations are low and cluster around the detection limit of the assay. Regardless, the mean amount of fentanyl delivered initially and the rate of increase were of similar magnitude irrespective of the frequency of transdermal dosing (i.e., hourly or 4-hourly).

Safety and Tolerability—All subjects received naltrexone to minimize the opioid effects of fentanyl. One subject reported nausea with the ET (fentanyl) hourly regimen. Three subjects reported adverse events during the ET (fentanyl) 4-hourly regimen (two reports of headache, and one each of abdominal pain and dizziness). Five subjects reported adverse effects during iv administration (one each of abdominal pain, constipation, nausea, asthenia, somnolence, erythema, and pruritus). No clinically significant alterations in vital signs were noted.

All the observed topical reactions 1, 6, and 24 h after system removal are summarized in Table 3. Erythema at the active gel site persisting at 24 h after system removal was comparable for both ET (fentanyl) regimens: no, or barely perceptible, erythema was evident for five subjects in the hourly regimen and six subjects in the 4-hourly regimen, while definite erythema was evident for four and three subjects, respectively. "Beet" redness was evident for one subject in the hourly regimen. No erythema was noted at the inactive gel site 24 h after system removal. The active gel site reactions are likely due to both drug and current.

Conclusion

The amount of fentanyl delivered to the systemic circulation per delivery period by the ET (fentanyl) system was estimated to be similar regardless of whether intermittent delivery was hourly or 4-hourly. About half the subjects reported either no, or barely perceptible, erythema at 24 h after system removal. Therefore, electronically controlled fentanyl delivery from the ET (fentanyl) system provided consistent drug delivery with either frequent or infrequent intermittent dosing. The skin reactions were tolerable, although, a larger study would be needed to assess them.

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