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Clinical Investigation

Biopharmaceutics of a New Transdermal Fentanyl Device

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Abstract

Background: Compared with conventional routes of delivering potent analgesics to postoperative patients, transdermal administration of fentanyl offers the advantages of simplicity and noninvasive delivery. The only available form of transdermal fentanyl, the Duragesic system, has been implicated in preventable patient deaths when used for postoperative analgesia and is contraindicated in the management of postoperative pain. We examined the biopharmaceutics of a new transdermal fentanyl device developed by Cygnus and intended for use as a postoperative analgesic to see whether the new formulation offers pharmacokinetic advantages that might permit safe use in postoperative patients.

Methods: We studied 15 consenting male adult surgical patients. Patients received 650 or 750 micro gram intravenous fentanyl as part of the induction of anesthesia. Plasma fentanyl concentrations were measured over the following 24-h period. On the first postoperative day, 24 h after the intravenous dose of fentanyl, a transdermal fentanyl device was placed on the upper torso of the patient for 24 h and then removed. Plasma fentanyl concentrations were measured for 72 h after application of the transdermal fentanyl device. From the concentration versus time profile for the 24 h after intravenous fentanyl administration we determined each patient's clearance and unit disposition function by moment analysis and constrained numeric deconvolution, respectively. From the concentration versus time profile for the 72 h after application of the transdermal device we determined the amount of fentanyl absorbed and the rate of absorption, again by moment analysis and constrained numeric deconvolution. The residual fentanyl in the transdermal fentanyl device was measured, permitting calculation of the absolute bioavailability of transdermally administered fentanyl.

Results: Of the 14 subjects who received transdermal fentanyl, 3 had clinically significant fentanyl toxicity, mandating early removal of the device. The range during the plateau from 12 to 24 h in subjects still wearing the device was 0.34-6.75 ng/ml, a 20-fold range in concentration. In subjects wearing the device for 24 h, the terminal half-life of fentanyl after removal of the device was 16 h. The bioavailability of transdermally administered fentanyl was 63 plus/minus 35% coefficient of variation. The rate of fentanyl absorption from 12-24 h ranged from 10 to 230 micro gram/h in subjects still wearing the device. In two subjects, the rate within the first 6 h briefly exceeded 300 micro gram/h. Both of these subjects demonstrated fentanyl toxicity, requiring early removal of the device.

Conclusions: The Cygnus transdermal fentanyl device shows great variability in the rate of fentanyl absorption, resulting in highly variable plasma fentanyl concentrations. Some persons may rapidly absorb fentanyl from the device in the first few hours after application, leading to fentanyl toxicity. The variability in effect of the Cygnus transdermal fentanyl device is appreciably greater than that reported for the currently available Duragesic transdermal fentanyl device, which is contraindicated for postoperative analgesia.

TRANSDERMAL drug delivery offers the potential benefits of simplicity, efficacy, and

patient acceptance. In theory, a transdermal delivery system may provide a stable plasma concentration for an extended period of time with acceptable interpatient variability. The physicochemical and physiologic principles governing transdermal drug absorption are well known and have been discussed elsewhere. [1-6].

In recent years increased interest in the treatment of acute and chronic pain has resulted in the development of transdermal delivery systems for analgesics. Administration of fentanyl by the transdermal route is appealing because fentanyl is a suitably potent analgesic agent the clinical pharmacologic characteristics of which are well understood. A transdermal fentanyl device (TFD), the Duragesic TFD, marketed by Janssen Pharmaceutica (Piscataway, NJ), has been approved for the treatment of chronic pain. [7] Janssen Pharmaceutica recently notified physicians that "[a] few isolated instances of misuse of Duragesic (fentanyl transdermal system) CII have been implicated in preventable patient deaths."* As a result, the package insert for Duragesic has been revised to state the following: "Because serious or life-threatening hypoventilation could occur, Duragesic is contraindicated in the management of acute or postoperative pain, including use in out-patient surgeries."**

The goal of this study was to determine the biopharmaceutics of a new TFD developed by Cygnus (Redwood City, CA). This device was specifically developed for postoperative analgesia and has been evaluated by Ohmeda Pharmaceutical (formerly Anaquest, Liberty Corner, NJ) for that purpose. [8] The design of the Cygnus TFD differs from the Duragesic TFD in that the Cygnus TFD does not incorporate a rate-controlling membrane. In our laboratory, we have previously determined the bioavailability and absorption profile of the Duragesic TFD. [9] In this study we performed a similar analysis of the biopharmaceutics of the Cygnus TFD. Determination of the biopharmaceutics of a transdermal drug delivery system is an essential step in rationally developing dosing guidelines for a new product.

Materials and Methods

The study was approved by the institutional review board. The study population consisted of 15 male patients at the Palo Alto Department of Veterans Affairs Medical Center scheduled for elective surgery. The median age was 62 yr (range 24-71 yr) and the median weight was 84 kg (range 66-100). Patients were recruited if the surgical procedure was expected (by us) to exceed 4 h, and to require a minimum of 4 days of hospitalization after surgery. Patients were excluded for a preoperative hemoglobin less than 11 g/dl, major systemic disease, or weight less than 50 kg or greater than 100 kg. The demographics are summarized in [Table 1](#).

Patient No.	Age (yr)	Weight (kg)	Surgery
1	67	66	Radical prostatectomy
2	71	76	Radical prostatectomy
3	65	86	Hemicolectomy
4	43	80	Total hip arthroplasty
5	27	100	Ankle reconstruction
6	65	96	Ankle fusion
7	24	89	Shoulder repair
8	63	86	Ventral herniorrhaphy
9	31	74	Splenectomy/pancreatectomy
11	66	98	Total knee arthroplasty
12	60	91	Cholecystectomy
13	54	82	Hemicolectomy
14	70	67	Thoracotomy
15	46	66	Total knee arthroplasty
Median	62	84	
Minimum	24	66	
Maximum	71	100	

Table 1

The study design was similar to that of Varvel et al. for the Duragesic TFD. [9] The patients received an intravenous infusion of fentanyl, 150 micro gram/min over a 5-min period on the first study day as part of the induction of general anesthesia. Arterial and, subsequently, venous blood samples were drawn at 1, 2, 3, 4, 5, 6, 7, 8, 10, 15, 30, 45, 60, 90, 120, 180, 240, 360, 480, 720, 960, 1,200, and 1,440 min for determination of plasma fentanyl concentration. The changeover from arterial to venous samples occurred when the patient left the recovery room after surgery, usually 6-8 h after fentanyl administration. Twenty-four hours later, a 60-cm [2] Cygnus TFD was placed on the upper torso of the patient. The area for application was previously prepared by clipping the hair with scissors and gently washing the skin with soap and water. After application that patient's blood pressure, heart rate, and ventilatory rate were recorded every hour. The TFD was removed if the ventilatory rate was less than 8 breaths/min for 5 min or the patient showed excessive sedation. Postoperative analgesia as well as supplementation during the patch application was provided by intramuscular administration of meperidine or morphine.

The TFD was left in place for 24 h. Venous blood samples were drawn at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 36, 48, 60, and 72 h after application of the TFD.

Pharmacokinetic Analysis: Intravenous Study

The terminal slope for each intravenous study was calculated by log-linear regression, based on a visual inspection of the data to determine where the log-linear phase began. The terminal half-life of each study was calculated as $\ln(2)/\text{terminal slope}_{IV}$, where IV = intravenous. The intercept was the $x = 0$ intercept determined by log-linear regression. The area under the curve for each intravenous study (AUC_{IV}) was calculated using linear trapezoids when concentrations were increasing, and log-linear trapezoids when concentrations were decreasing. The AUC_{IV} extrapolation from the observation at 1,440 min to infinity was calculated as $\text{intercept}_{IV} \times e^{\text{sup-terminal slope}_{IV} \times 1,440} / \text{terminal slope}_{IV}$. The extrapolation was based on $\text{intercept}_{IV} \times e^{\text{sup-terminal slope}_{IV} \times 1,440}$ rather than the last observation to avoid placing excessive weight on the last observation, which frequently was barely above the limits of quantitation of the assay. If the value at 1,440 was less than the limits of quantitation of the assay, then the analysis of the terminal AUC proceeded from the time of the last measured concentration above the limit of quantitation. The percentage AUC_{IV} under the data was calculated as the percentage of the cumulative AUC_{IV} from time 0 to the time of the last observation as a percentage of the total AUC_{IV} . Clearance (liters per hour) was calculated as $\text{dose}_{IV} / AUC_{IV} \times 60$.

For this study, we did not perform nonlinear regression. Instead, we used constrained

numeric deconvolution to calculate the fentanyl unit disposition function in each subject using the software developed by Verotta et al. [10] and modified by the one of the authors (S.L.S.) to approximate more closely the logarithmic shape of the unit disposition function. The values of the unit disposition function over time were not of particular interest but were an intermediate step in the calculation of the rate or absorption over time, as described below. However, we compared the value of clearance based on the UDF, calculated as $1/[\int_0^{\infty} \text{unit disposition function (UDF)}]$ with the value of clearance calculated as $\text{dose}_{\text{IV}}/\text{AUC}_{\text{IV}}$ to verify the numeric deconvolution approach.

Because the concentrations and pharmacokinetic parameters cannot be negative, the analyses assumed log-normal distribution of concentrations at each point in time, and log-normal distribution of each of the pharmacokinetic parameters.

The log mean was calculated as $e^{\sup [\sum_{i=1}^n \ln(\text{parameter}_i)]/n}$ and the variability about this was calculated as $\sqrt{\{n [\sum_{i=1}^n \ln(\text{parameter}_i)]^2 - [\sum_{i=1}^n \ln(\text{parameter}_i)]^2\}/n(n-1)}$. In the log domain, this is the SD. For small values (e.g., approximately less than 0.50) the SD in the log domain approximates the coefficient of variation (CV) in the standard domain and is given as a percentage.

Transdermal Fentanyl Analysis

In patients 3, 8, 12, and 13, there was a small but measurable fentanyl concentration at the time the TFD was placed, 24 h after the intravenous dose. To remove the influence of this residual fentanyl, the terminal slope from the intravenous study was extrapolated for the full 72 h of the transdermal study, and the fentanyl concentrations from the intravenous study were subtracted from the observed fentanyl concentrations. The amount subtracted was $\text{intercept}_{\text{IV}} \times e^{-\text{terminal slope}_{\text{IV}} \times \text{time}}$. The adjustment was uniformly small, and less than the limits of quantitation of the assay by 4 h in all but 1 subject. [11] The figures show the actual fentanyl concentrations, not the adjusted concentrations. However, the analyses described below were based on the adjusted concentrations to more accurately calculate the true rate of fentanyl infusion from the TFD.

The terminal slope for each transdermal study was calculated by log-linear regression, based on a visual inspection of the data to determine where the log-linear phase began. The terminal half-life of each study was simply $\ln(2)/\text{terminal slope}_{\text{TD}}$, where TD = transdermal.

In several subjects there was an initial "rapid" phase to the washout, and so the slope was calculated from the data points beginning several hours after the TFD was removed. The intercept was the $x = 0$ intercept determined by log-linear regression. The area under the curve for each transdermal study (AUC_{TD}) was calculated using linear trapezoids when concentrations were increasing, and log-linear trapezoids when concentrations were

decreasing. As described for the intravenous dose, the AUC extrapolation from the observation at 72 h to infinity was calculated as $\text{intercept}_{\text{TD}} \times e^{\text{sup-terminal slope}_{\text{TD}} \times 72 / \text{terminal slope}_{\text{TD}}}$. The extrapolation was based on $\text{intercept}_{\text{TD}} \times e^{\text{sup-terminal slope}_{\text{TD}} \times 72}$ rather than the last observation to avoid placing excessive weight on the last observation. The dose_{TD} is the amount of fentanyl delivered to the systemic circulation. The dose_{TD} was calculated as $\text{AUC}_{\text{TD}} \times \text{clearance}_{\text{IV}}$.

The initial fentanyl content of the Cygnus TFD was 9,120 micro gram. The residual fentanyl content in each TFD was measured by Cygnus. The difference between the initial and residual fentanyl contents is the amount of fentanyl leaving the TFD during the 24 application period. This difference we called the "Delta content." The bioavailability is, by definition, the fraction of this Delta content that was absorbed systemically, calculated as $\text{dose}_{\text{TD}} / \text{Delta content} \times 100\%$.

As was previously described for the intravenous pharmacokinetics, if we assume that the pharmacokinetics are linear then the concentrations over time after any input represent the convolution of the input function with the disposition function. For transdermal fentanyl, the input function is the rate of fentanyl transfer to the systemic circulation. This rate of transfer cannot be directly measured. However, if we know the plasma concentrations over time after transdermal application, and we know the disposition function from the intravenous study, we can use deconvolution to compute the input function, which is the rate of absorption over time.

We calculated the rate of systemic fentanyl absorption using constrained numeric deconvolution of the adjusted fentanyl concentrations over time against the previously calculated disposition function for each subject, calculated as described above from the intravenous fentanyl pharmacokinetics. The calculated rate of systemic absorption from the Cygnus TFD was constrained to be positive at all times (i.e., the patch cannot remove drug from the body). Rates of absorption were calculated for each subject, regardless of when the TFD was removed and reported using simple average and SD.

Assay

Fentanyl was assayed as described by Michiels et al. [\[12\]](#) using precalibrated bulk solutions of [³H]fentanyl tracer (Research Diagnostics, Flanders, NJ) and fentanyl antiserum (Research Diagnostics) to increase consistency. After collection into heparinized containers, the blood was centrifuged and the plasma was transferred to glass tubes. The samples were frozen at -18 degrees Fahrenheit until assay. At the time of the assay the samples were thawed and clotted protein was removed. Paired 100-micro liter aliquots were removed and transferred to 1.5-ml polypropylene microfuge tubes. Six hundred microliters dilute fentanyl tracer solution and 100 micro liter fentanyl antiserum were added to each tube, and the tubes were vortexed. After overnight incubation, 200 micro liter phosphate

buffer (Endocrine Sciences) and a dextran-coated activated charcoal pellet (40 mg, DCC402, Westchem) were added. The tubes were vortexed and then centrifuged at 8,800g for 13 min. Eight hundred microliters of supernatant was removed and placed in a glass scintillation vial containing 5.5 ml Beta-Blend (ICN Radio-chemicals, Irvine, CA) and vortexed. The scintillation vials were placed in a Beckman 5801 scintillation counter with calibration, standard, and quality-control tubes (Beckman Instruments, Fullerton, CA). The scintillations were analyzed using the Immunofit software developed by Beckman Instruments. If recovery of the quality-control samples differed from the known values by more than 15%, the entire assay was repeated. If the difference between the paired aliquots differed by more than 5%, the individual samples were reanalyzed. The limit of quantitation and detection of the assay were 0.20 and 0.05 ng/ml, respectively. The variability in quality-control recovery was less than 5%.

Results

Intravenous Study (First 24 h)

Because of an incorrectly positioned safety stop on the infusion pump subjects 2 and 3 received only 650 micro gram fentanyl. This did not affect our analysis of the biopharmaceutics of the Cygnus TFD in these subjects, but we did exclude their concentrations from the calculation of log-mean fentanyl concentration during the intravenous portion of the study ([Figure 1](#)). Subject 10 withdrew from the study before placement of the Cygnus TFD. The samples from the intravenous portion of the study were discarded and no further analysis was performed.

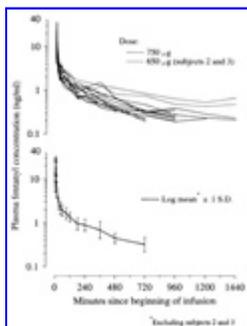


Figure 1

Five plasma fentanyl concentrations were deleted from the analysis. These concentrations were drawn at 360 or 480 min, and represented the first sample drawn from the intravenous catheter. In each case, the fentanyl concentration was a full order of magnitude greater than either the earlier arterial or the subsequent venous sample. We did not expect that 6-8 h after the intravenous fentanyl dose there would be any residual fentanyl associated with the catheter, but somehow a small amount of fentanyl was sequestered in some space within the catheter, and was withdrawn with the first venous sample. Subsequent venous samples were invariably consistent with the plasma fentanyl time course of the earlier arterial samples, and thus the loss of the first venous sample did not affect the data analysis.

([Figure 1](#)) shows the plasma concentrations over time after intravenous drug administration. The top graph shows the concentrations in all subjects, and the bottom graph shows the log mean plus/minus 1 SD in the log domain for subjects receiving 750 micro gram. The average CV in fentanyl concentration after intravenous administration was 35%.

([Table 2](#)) summarizes the pharmacokinetic results from the intravenous portion of the study. The terminal half-life for intravenous fentanyl in this study ranged from 225 to 778 min. The log-mean terminal half-life was 411 min plus/minus 38% CV. The average AUC, extrapolated to infinity, was 1,005 ng *symbol* min *symbol* ml sup -1 plus/minus 34% CV. Eighty-five percent of the AUC was under the observations, suggesting that the estimates of clearance are likely to be accurate. The mean clearance was 44 l/h plus/minus 35% CV. This is nearly identical with the fentanyl clearance of 46 l/h reported by Varvel and colleagues in their analysis of the biopharmaceutics of the Duragesic TFD. [\[9\]](#).

Table 2

([Figure 2](#)) shows the individual unit disposition functions in the 14 subjects (top graph) and the log-mean and SDs for the group (bottom graph). The average CV in the unit disposition functions was 40%, modestly greater than the mean CV of 35% for the intravenous concentrations. This greater CV is expected because numeric deconvolution tends to amplify noise. The clearance calculated from the unit disposition, 45 l/h, was nearly identical with the average clearance calculated from the moment analysis, 44 l/h.

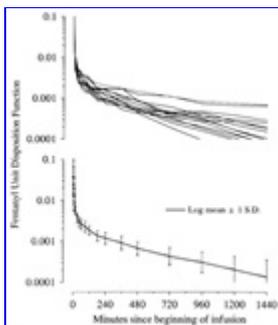


Figure 2

Transdermal Pharmacokinetics (24-96 h)

The Cygnus TFD was removed from three subjects before completion of the study for clinical problems. The fentanyl concentrations in subject 2 increased from undetectable at time 0 to 3.0 ng/ml at 2 h, resulting in sedation and ventilatory depression. At 4 h the Cygnus TFD was removed, and the patient given 160 micro gram naloxone in divided doses in addition to supplemental oxygen (facial mask, 4 l/min). The fentanyl concentration at that time was 2.9

ng/ml. At 6 h after application the patient still required intermittent doses (120 micro gram total) of naloxone, and his plasma fentanyl concentrations remained increased at 2.9 ng/ml.

The Cygnus TFD was removed from subject 13 after 9 h, at his request, because he felt "dizzy." He did not exhibit respiratory depression at the time. However, his plasma fentanyl concentration at 9 h was 5.05 ng/ml, confirming an overdose. The Cygnus TFD was removed from subject 14 at 23 h 15 min. This subject demonstrated respiratory depression at that time. His plasma fentanyl concentration at 24 h was 3.22 ng/ml. Subjects 2 and 13 were not included in the bioavailability analysis because the TFD was removed very early. Subject 14 completed 95% of the study, and thus was included in the bioavailability analysis.

A terminal slope could not be calculated for subject 6 because his fentanyl concentrations decreased to less than the limits of quantification at 36 h. Therefore this subject was excluded from the AUC sub TD and bioavailability analyses but not from calculations of the log-mean concentrations over time (Figure 3, bottom graph). Subject 9 underwent a pancreatectomy/splenectomy. This subject had concentrations ranging from 4.25 to 6.75 ng/ml during the interval from 6 to 24 h after transdermal fentanyl application and a calculated bioavailability of 191%. This subject did not show signs of fentanyl toxicity. It is impossible to have a bioavailability in excess of 100%, and so subject 9 likely had reduced fentanyl clearance in the postoperatively, explaining both the high fentanyl concentrations and a transdermal fentanyl bioavailability exceeding 100%. Given the nature of this operation, it seems likely that his liver was acutely injured during surgery, substantially reducing his fentanyl clearance. Thus, subject 9 was excluded from the bioavailability analysis. However, because this may not be an unlikely perioperative event, his concentrations are included in the calculation of the log-mean fentanyl concentrations over time (Figure 3, bottom graph).

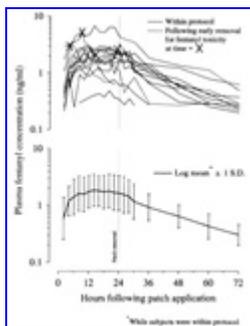


Figure 3

(Figure 3) shows the plasma fentanyl concentrations during and after application of the Cygnus TFD. The concentrations after premature removal of the Cygnus TFD are shown as dashed lines. During the "plateau" phase from 12-24 h, the log-mean concentrations ranged from 1.74 ng/ml at 12 to 1.64 ng/ml at 24 h. Thus, on average, the Cygnus TFD maintained a constant plateau from 12 h until removal at 24 h. However, during the plateau the fentanyl concentration in subjects still wearing the Cygnus TFD ranged from 0.34 to 6.75 ng/ml, a 20-fold range. The average CV during the plateau was 65%, almost twice the variability after

intravenous fentanyl administration. In addition, the variability calculations do not include concentrations after premature TFD removal. Had those subjects worn the TFD for the full 24 h, it is likely that the CV would have been even greater than we report.

(Table 3) summarizes the pharmacokinetics of the Cygnus TFD. The calculations of the log mean and percentage CV exclude subjects 2, 6, 9, and 13 as explained above. The terminal slope ranged from 0.023 to 0.071 h sup -1, with a log mean of 0.044 h sup -1 plus/minus 31% CV. The terminal half-life for transdermal fentanyl in this study ranged from 10 to 30 h. The log-mean half-life was 16 h plus/minus 31%. The log average AUC, extrapolated to infinity, was 73 ng *symbol* h *symbol* ml sup -1 plus/minus 36%, and 91 plus/minus 7% of the AUC was less than the observed fentanyl concentrations.

Table 3

The residual content of the TFD was not assayed for subject 15. Excluding subjects 2, 6, 9, 13 and 15, the log-mean dose of fentanyl delivered by the Cygnus TFD to the systemic circulation was 2,977 micro gram plus/minus 29% CV. The log-mean residual content, as measured by Cygnus, was 4,412 micro gram plus/minus 22% CV. The log-mean delta content was 4,539 micro gram plus/minus 19% CV. The bioavailability of fentanyl to the systemic circulation ranged from 36% to 101%. The log-mean bioavailability was 63 plus/minus 35% CV.

The absorption rates for each subject are shown in the top graph of Figure 4, and the bottom graph shows the average absorption rate plus/minus 1 SD. There was considerable variability in the time course and rate of absorption. The rate of fentanyl absorption from 12-24 h ranged from 10 to 230 micro gram/h in subjects still wearing the device. In 2 subjects the absorption rate rapidly increased to more than 300 micro gram/h, resulting in fentanyl toxicity and requiring early removal of the Cygnus TFD. The average rate of fentanyl absorption peaked 8 h after application of the TFD application at 107 micro gram/h plus/minus 61% CV. The absorption rate then steadily decreased to 55 micro gram/h at 22 h, and increased to 80 micro gram/h at 24 h when the TFD was removed. After removal of the TFD there was continued absorption from the cutaneous depot in all subjects.

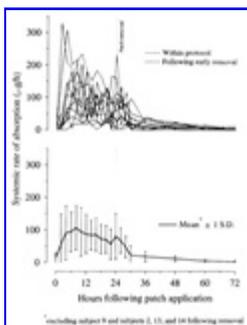


Figure 4

Discussion

Safety

Although this study was not specifically designed to evaluate the safety of the Cygnus TFD, it is concerning that in two subjects the fentanyl concentrations increased alarmingly fast, requiring that the TFD be removed early. Subject 2 had profound ventilatory depression, requiring multiple doses of naloxone over a 2-h period. Subject 13 complained of dizziness, causing us to remove his TFD 9 h after application. A third patient, subject 14, demonstrated ventilatory depression at 23 h associated with a concentration of 3.22 ng/ml at 24 h. These experiences suggest that the Cygnus 60 cm² TFD can infuse fentanyl at rates that are unacceptably great.

In a clinical study of patients undergoing gynecologic exploratory laparotomy, Miguel et al. [8] used the 60-cm² patch to provide postoperative pain relief. Patients were also allowed to use supplemental patient-controlled morphine. They found an incidence of respiratory depression of 16% occurring in average 11 h after patch placement. Fentanyl plasma concentrations were 5.6 ng/ml in two of these patients and 5.8 ng/ml in a third. In patients receiving fentanyl by a 40-cm² device, they also found a 6% incidence of respiratory depression.

Intravenous Pharmacokinetics

This study design assumes that the clearance and unit disposition function for fentanyl during the intravenous portion of the study be consistent with the clearance and unit disposition function for fentanyl during the subsequent transdermal portion of the study. Anesthesia is associated with changes in cardiac output and liver blood flow, and it is likely that the pharmacokinetics of fentanyl were perturbed by the anesthesia and surgery during the intravenous portion of the study. However, the terminal half life of 411 min is consistent with that reported by Varvel et al., [9] Scott and Stanski, [11] and Shafer et al. [13] In addition, the mean CVs for the measured plasma drug concentrations and the calculated UDF after intravenous injection were 35% and 40%, respectively. These are very reasonable estimates of fentanyl pharmacokinetic variability, particularly in a population of elderly veterans, and would suggest that there were not dramatic disturbances in fentanyl pharmacokinetics from the anesthesia and surgery that coincided with the intravenous portion of the study.

Compared with Varvel et al.'s study, [9] our population was less homogeneous. As shown in Table 1, 6 of our patients underwent major intraabdominal surgery with retraction of the liver and major abdominal organs. This theoretically could cause an additional reduction in liver blood flow and affect fentanyl clearance. We divided our population in two groups: patients undergoing intraabdominal surgery and patients undergoing other procedures with

no manipulation of abdominal content and compared fentanyl clearances. We found no statistical differences between the two groups.

Thus, the intravenous pharmacokinetic portion of this study was mostly unremarkable, and consistent with previously reported fentanyl pharmacokinetic studies.

Transdermal Pharmacokinetics

This study design requires that the clearance of fentanyl during on the operative day be identical with the clearance of fentanyl during the first 3 postoperative days. Surgery and anesthesia do affect liver blood flow, but we are unaware of any data showing the fentanyl clearance per se is altered by anesthesia and surgery. Shafer et al. [13] compared the pharmacokinetics of fentanyl determined in surgical patients with the pharmacokinetics of fentanyl determined by McClain and Hug in volunteers. [14] Shafer et al. [13] found that the from 10 to 480 min (the duration of sampling in McClain and Hug's study) the predicted fentanyl concentrations based on pharmacokinetics derived from surgical patients were almost identical with the predicted concentrations derived from volunteers. Thus, the assumption that fentanyl clearance remains constant appears reasonable. The alternative would be to administer 750 micro gram fentanyl to volunteers on day 1, and transdermal fentanyl to the same volunteers on day 2. However, such a volunteer study raises ethical concerns because of the risk of acute ventilatory depression from the intravenous dose of fentanyl, and the risk of opioid addiction after 2 days of sustained fentanyl administration.

In this study we observed fentanyl in the plasma from the intravenous dose at the time the Cygnus TFD was applied to the patient. In our prior study of the Duragesic TFD we ignored the small fentanyl in the plasma when the TFD was applied. In retrospect, that analysis might have benefited from a similar adjustment in that analysis and subtracted out the residual effects of the intravenous study.

The 16 h terminal half-life after removal of the Cygnus TFD far exceeded the terminal half-life of approximately 7 h observed after intravenous administration. This prolonged terminal half-life suggests that continued absorption from a cutaneous depot primarily controls the rate of decline in plasma concentrations after removal of the TFD. The rate of this continued absorption can be seen in [Figure 4](#) after removal of the TFD at 24 h. Varvel and colleagues reported a terminal half-life after removal of the Duragesic TFD of 17 h. [9] The nearly identical results suggest that the rate of fentanyl absorption after removal of the TFD is a function of the physicochemical and physiologic properties of the subcutaneous depot, and is independent of the TFD itself.

Although the variability in absorption rate is great, this must be interpreted with some caution. The absorption rates were calculated by deconvolution of the adjusted transdermal fentanyl concentrations against the unit disposition function determined from the intravenous fentanyl study. Thus, the deconvolution that calculated the rate of absorption used the result of a previous numeric deconvolution (the intravenous disposition function)

as one of the entered functions. Deconvolution tends to amplify noise. The noise in the intravenous data were slightly amplified during the constrained numeric deconvolution, as suggested by the increase in CV from 35% for the original fentanyl concentration to 40% for the unit disposition function. The noise was likely further amplified during the second deconvolution step that determined the rate of absorption. However, the great variability seen in absorption rates mirrors the great variability seen in the actual fentanyl concentrations after application of the Cygnus TFD. Thus, we believe that most of the variability in absorption rate reflects true underlying variability in fentanyl absorption into the systemic circulation.

We were able to perform bioavailability analysis on only 9 of the 14 subjects who received transdermal fentanyl. Of the 5 subjects excluded, 2 were excluded because the TFD was prematurely removed because of fentanyl toxicity (subjects 2 and 13); 1 was excluded because of concentrations so low that an AUC could not be calculated (subject 6); 1 was excluded because of very high concentrations that could be explained only by an alteration in fentanyl clearance (subject 9); and 1 was excluded simply because the residual fentanyl content in the patch was not assayed (subject 15). Although we were chagrined that in so many subjects the bioavailability could not be evaluated, this problem primarily reflected the great variability in absorption rate of the Cygnus TFD and not the study design itself. In a nearly identical study design, Varvel et al. [9] had no subjects in whom the bioavailability could not be calculated.

The bioavailability of 63% suggests that 37% of the fentanyl that leaves the Cygnus TFD does not subsequently appear in the systemic circulation. This drug could conceivably be metabolized by the skin, as has been demonstrated for nitroglycerin. [15] However, there no cutaneous metabolism of fentanyl has been demonstrated. Alternative explanations for the low bioavailability are metabolism by cutaneous bacteria, sequestration in the stratum corneum, loss from the TFD into the environment via sweat and possible errors in the determination of initial or residual TFD fentanyl content. Varvel et al. reported that the bioavailability of transdermal fentanyl administered with the Duragesic TFD was 92%. [9] We cannot explain why the bioavailability of the Cygnus TFD was so much less, especially considering that both studies were conducted using nearly identical study designs by our research group at Stanford.

Comparison with the Duragesic Transdermal Fentanyl Device

The Duragesic TFD has been approved for chronic pain, but is contraindicated for acute postoperative analgesia because of concern over potential toxicity. As the Cygnus TFD was developed to for postoperative analgesia, it is instructive to compare the biopharmaceutics of the two TFDs:

1. The Duragesic TFD produced a 4-fold range in concentrations during the plateau, 1-4 ng/ml, whereas the Cygnus TFD produced a 20-fold range in concentrations during the plateau, 0.34-6.75 ng/ml. Varvel et al. concluded that the Duragesic TFD added little

additional variability to the intrinsic variability observed with fentanyl pharmacokinetics. [\[9\]](#)
In contrast, the variability observed in fentanyl concentrations after application of the Cygnus TFD was twice that observed from the intravenous administration of fentanyl.

2. The rate of absorption from the Duragesic TFD remained fairly constant at 90 micro gram/h from 16 to 24 h. The rate of absorption from the Cygnus TFD declined from an average rate of 107 micro gram/h at 12 h to an average rate of 55 micro gram/h at 22 h.

3. No subjects in the Duragesic TFD study experienced the very rapid onset of high concentrations seen in two of the patients from the current study, and no subjects experienced ventilatory depression, despite a greater average rate of fentanyl delivery during the period from 12 to 24 h (90 micro gram/h for the Duragesic versus 76 micro gram/h for the Cygnus TFD).

The Duragesic TFD contains a rate-controlling membrane that contributes approximately 50% of the resistance to fentanyl flux across the skin, the other 50% being contributed by the stratum corneum. [\[16\]](#) If the stratum corneum has been stripped from the skin (as can easily happen from a single application of adhesive tape, for example), the resistance to fentanyl flow can thus decrease by no more than 50%. The Cygnus TFD has no such rate-controlling membrane. As a result, the Cygnus TFD depends almost entirely on the stratum corneum to limit the rate of fentanyl flow. If the stratum corneum has been stripped, then the resistance to fentanyl flow can decrease substantially. In those subjects in whom the fentanyl concentrations increased rapidly, we may have placed the Cygnus TFD over a portion of skin stripped of stratum corneum from the casual application of adhesive tape to the patient during surgery. Because stripped skin looks like normal skin, there is no way to tell at the time of application whether the Cygnus TFD was placed on intact stratum corneum. Thus, the great variability in absorption rate and fentanyl concentration, and the very rapid fentanyl absorption in some patients, is an expected consequence of the design of the Cygnus TFD.

In conclusion, the use of the Duragesic TFD has been implicated in serious complications, including death, in postoperative patients. Janssen Pharmaceutica, in concert with the Food and Drug Administration, has elected to contraindicate absolutely the Duragesic TFD for use as a postoperative analgesic. Given the greater variability in absorption rate observed with the Cygnus TFD and the tendency toward very rapid early absorption in some persons, the biopharmaceutic characteristics of the Cygnus TFD do not suggest that it affords greater safety as a TFD for postoperative analgesia.

* Clausner MA: Letter to medical professionals. Piscataway, NJ, Medical Affairs, Janssen Pharmaceutica, January 17, 1994.

** Duragesic (fentanyl transdermal system) CII package insert. Piscataway, NJ, Janssen Pharmaceutica, January 1994.

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