A Double-blind, Placebo-controlled Trial of Transdermal Fentanyl after Abdominal Hysterectomy

Analgesic, Respiratory, and Pharmacokinetic Effects

Alan N. Sandler, M.B., Ch.B., F.R.C.P.C.,* Alan D. Baxter, M.B., Ch.B., F.R.C.P.C.,† Joel Katz, Ph.D.,‡ Benoit Samson, M.D., F.R.C.P.C.,§ Mark Friedlander, M.B., Ch.B., F.R.C.P.C.,‖ Peter Norman, M.D., F.R.C.P.C.,# Gideon Koren, M.D., F.R.C.P.C.,** Sandra Roger, R.N.,†† Kathryn Hull, R.N.,‡‡ Julia Klein, M.Sc.§§

Background: **A randomized, double-blind, placebo-controlled trial was conducted to assess the analgesic, pharmacokinetic, and clinical respiratory effects of 72-h application of two transdermal fentanyl (TTSF) patch sizes in patients undergoing abdominal hysterectomy.**

Methods: **TTSF patches releasing 50 μg/h (TTSF-50) or 75 μg/h (TTSF-75) fentanyl or placebo patches were applied to 120 women 2 h before abdominal hysterectomy under general anesthesia. Postoperatively, all patients had access to supplemental morphine using patient-controlled analgesia pumps. Each patient was attended continuously by a research nurse for 8 h on the night before surgery and for 84 h after patch application. The following data were collected: visual analog scale pain scores, supplementary analgesia, fentanyl plasma concentration (4-h intervals), continuous hemoglobin saturation (pulse oximetry), respiratory pattern (continuous respiratory inductive plethysmography), and adverse effects (nausea, vomiting, pruritus). Data analysis included analysis of variance, Kruskal-Wallis, and chi-squared. $P < 0.05$ was considered significant.**

Results: **There were no demographic differences among groups. Visual analog scale pain scores were significantly lower for the TTSF-75 group, and supplemental morphine was significantly decreased in the TTSF-75 group in the postanesthesia care unit and for both the TTSF-50 and the TTSF-75 group for 8–48 h postoperatively. Between 5 and 36 h, the TTSF groups had significantly increased abnormal respiratory pattern including apneic episodes (tidal volume of less than 100 ml for more than 15 s) and episodes of slow respiratory rate (less than 8 breaths/min persisting for more than 5 min) and significantly increased requirement for oxygen supplementation. Nine patients in the TTSF groups were withdrawn because of severe respiratory depression compared to none in the placebo group. No significant between-group differences were present in the incidence of nausea, vomiting, or pruritus. Although fentanyl plasma concentration was higher in the TTSF-75 group than in the TTSF-50 group, the differences were not significant. Fentanyl plasma concentration decreased significantly 48 h after patch application.**

Conclusions: **Application of TTSF patches 2 h preoperatively is associated with moderate supplementary opioid requirements for analgesia in the early postoperative period and ongoing opioid supplementation for at least 72 h. Although good analgesia is the result of this combination therapy, it is associated with a high incidence of respiratory depression requiring intensive monitoring, oxygen supplementation, removal of the TTSF patches in approximately 11% of the patients, and opioid reversal with naloxone in approximately**

* Associate Professor, Department of Anesthesia, University of Toronto; Anesthetist-in-Chief and Director, Acute Pain Research Unit, The Toronto Hospital.

† Associate Professor, Department of Anesthesia, University of Ottawa.

‡ Assistant Professor, Departments of Behavioral Science and Anesthesia, University of Toronto; Medical Research Council of Canada Scholar, Department of Psychology, Toronto General Division, The Toronto Hospital.

§ Assistant Professor, Department of Anesthesia, University of Ottawa.

‖ Lecturer, Department of Anesthesia, University of Toronto.

Assistant Professor, Department of Anesthesia, University of Toronto.

** Professor of Clinical Pharmacology, Hospital for Sick Children, University of Toronto.

†† Research Nurse in Anesthesia, Department of Anesthesia, The Toronto Hospital.

‡‡ Research Nurse in Anesthesia, Department of Anesthesia, Ottawa General Hospital.

§§ Research Associate, Department of Clinical Pharmacology, Hospital for Sick Children.

8% of the patients. (Key words: Analgesia: patient-controlled; postoperative; transdermal delivery. Complications: respiratory depression. Opioids: basal infusion; fentanyl. Pain: postoperative. Ventilation, apnea: pattern.)

THE combination of the Transdermal Therapeutic System[1] (TTS, Alza, Palo Alto, CA) with the lipid-soluble synthetic opioid fentanyl provided a simple, effective transdermal delivery system for a potent opioid analgesic. The system controls release of fentanyl to provide a continuous and steady supply of the opioid transdermally[2] and maintains relatively predictable plasma concentrations of fentanyl without invasive procedures or special equipment.[3] The variation in patient metabolic clearance and steady-state volume of distribution will determine the resulting steady-state plasma concentration in each subject. Drug delivery is increased by increasing the size of the active patch surface as each square centimeter delivers approximately 2.5 μg/h fentanyl. Thus, a 20-cm^2 patch delivers 50 μg/h and a 30-cm^2 patch 75 μg/h. Earlier clinical studies documented the analgesic effectiveness of various sizes of TTSF patches (*e.g.,* 50, 75, and 100 μg/h) for the treatment of postoperative pain after orthopedic,[4–8] urologic,[9] gynecologic,[10] abdominal,[11–13] and thoracic surgery.[6] Most of these studies involved patch application of 24 h or less with a small number of studies assessing patch use over longer periods (up to 72 h). The choice of administered dose should result in fentanyl plasma concentrations that are safe in all patients, *i.e.,* no risk of respiratory depression; this will result in incomplete analgesic efficacy in some patients because of pharmacokinetic variability. Thus, the supplementation of morphine (or other analgesics) is a fundamental component of the use of transdermal fentanyl patch in some patients. A common finding in previous studies was the requirement for supplementary analgesics in addition to the TTSF patch in the postoperative period.[14] Despite using relatively low-dose TTSF patches that often required opioid supplementation, several investigators still reported a relatively low incidence of clinically significant respiratory depression in their patients receiving TTSF[4,5,11,13,14] using mostly noncontinuous methods to measure respiratory depression. Therefore, we elected to further investigate the use of the TTSF patch to define the incidence and severity of clinically significant respiratory depression with its use. Thus, this study was undertaken to evaluate 50 and 75 μg/h TTSF used for 72 h after abdominal hysterectomy. Postoperative analgesia, supplementary opioid requirements using patient-controlled analgesia (PCA), serial plasma fentanyl concentration, and particularly intensive noninvasive continuous respiratory monitoring (pulse oximetry, respiratory inductive plethysmography) were measured for 84 h after surgery to determine the analgesic effectiveness and the respiratory effects of the TTSF patch.

Methods and Materials

Approval to carry out this study was obtained from the Toronto Hospital and Ottawa General Hospital Committees for Research on Human Subjects. All patients gave their written informed consent to participate before entering the study. The study was designed to be randomized, double-blind, and placebo-controlled.

Sample Size Estimation. Based on the results of previous studies,[4,15] it was determined that, in a three-arm study comparing placebo, TTSF-50, and TTSF-75, a sample size of 40 patients per group would provide a type 1 error rate of 0.05 and a type 2 error rate of 0.1 (*i.e.,* power of 90%) to detect a mean difference in morphine use of 6 mg during the period from 12 to 24 h after TTS application. This difference applied to comparisons between each of the two active groups and the placebo group.

Patient Selection. Patients scheduled for abdominal hysterectomy were included in the study. Inclusion criteria were age 18–60 yr; ASA physical status 1 or 2; body weight 50–75 kg; no significant central nervous system, respiratory, cardiac, hepatic, or renal dysfunction; no previous allergies or adverse reactions with opioid analgesics; and no history of opioid or substance abuse.

Randomization and Blinding Procedures. Patients were randomly assigned to one of three groups, placebo, TTSF-50, or TTSF-75. Double-blinding was achieved by applying two unmarked patches to each patient, one of TTSF-50 size and the other of TTSF-75 size. Active patches containing fentanyl were indistinguishable from placebo patches.

Preoperative Assessment. The night before surgery, patients were familiarized with the visual analog scale (VAS) and were introduced to the PCA pump and instructed in its use. To provide baseline measurements for postoperative respiratory assessment, all subjects underwent a modified sleep study for 8 h on the preoperative night. Respiratory pattern was assessed continuously with respiratory inductive plethysmography (NIMS, Miami Beach, FL), and hemoglobin oxygen saturation (Sp_{O_2}) was continuously measured using pulse

oximetry (Nellcor N-100, Nellcor, Hayward, Ca) while patients slept. Calibration and validation of the respiratory inductive plethysmograph—as well as its application in previous postoperative analgesic studies—have been described elsewhere.[16-18] Respiratory rate (RR), episodes of apnea (tidal volume of less than 100 ml for more than 15 s), and episodes of slow RR (SRR, less than 8 breaths/min persisting for more than 5 min) were measured continuously and recorded in 5-min epochs. Patients were attended continuously by trained personnel during the entire 8-h preoperative and 84-h postoperative data collection periods. Respiratory pattern abnormalities were confirmed by the analysis of real-time respiratory inductive plethysmography output and direct observation of the patient. Revalidation (spirobag technique) was performed several times during the observation periods and recalibration instituted if the error was greater than 20%.

Patch Application. The patches were applied immediately below the clavicle on the right and left sides of the upper chest approximately 2 h before surgery. The time of patch application was taken as time 0 for all measurements.

Anesthesia. All patients received 10 mg oral diazepam 2 h preoperatively. Anesthesia was induced with sodium thiopental and maintained with 0.5 μg/kg sufentanil, oxygen/nitrous oxide, and isoflurane plus pancuronium for muscle relaxation. At the conclusion of surgery, muscle relaxation was reversed with neostigmine and atropine. With resumption of spontaneous breathing, the trachea was extubated, and the patient was transported to the postanesthesia care unit (PACU).

Postoperative Management

Supplementary Analgesia. The patches were left *in situ* for 72 h after application. Patients were monitored and data collected for the full 72 h period of patch application plus an additional 12 h after patch removal. Supplementary analgesia consisted of observer-administered morphine boluses in the PACU and PCA morphine upon transfer to the ward. In the PACU, if the patient spontaneously requested analgesia, a 2-mg dose of intravenous morphine was given. In addition, at 10-min intervals, the patient was asked, "Do you need pain relief?" If a positive response was given, a 2-mg intravenous dose of morphine was administered. The PCA pump (Abbott Life Care Infuser, Chicago, IL) was set to deliver a 1-mg bolus of morphine with a lockout time of 5 min. The total dose of morphine required during the past hour was recorded hourly.

Postoperative Pain and Sedation Measurement. A 10-cm VAS with 0 = no pain and 10 = worst pain imaginable, was used to assess pain intensity at rest and with movement. Pain was measured every 4 h unless the patient was asleep. A three-point sedation scale was recorded every 4 h unless the patient was asleep (0 = alert, oriented; 1 = drowsy, oriented; 2 = drowsy, disoriented). No more than 8 h was allowed to elapse between two consecutive measurements, which occasionally required waking the patient.

Pharmacokinetic Analysis. Immediately before the application of the TTS patches and every 4 h postoperatively, venous blood samples were drawn from a peripheral vein (*via* an indwelling heparinized cannula where possible) for plasma fentanyl assay. Plasma fentanyl concentrations were determined with a commercial radioimmunoassay kit[19] (Janssen, Beerse, The Netherlands). In our laboratory, the assay is sensitive to 0.1 ng/ml, with intraassay and interassay coefficients of variation of 6.0% and 6.9%, respectively, at 1.0 ng/ml.

Postoperative Respiratory Monitoring. When the patient arrived in the PACU, respiratory inductive plethysmography and pulse oximetry monitoring was reinstituted and continued until the end of the study. Oxygen supplementation routinely was provided for the first 2 h in the PACU and then discontinued. If, at any time, respiration was judged to be inadequate (RR < 8 breaths/min × 3 episodes/h) and/or hemoglobin saturation was <90%, an arterial blood gas sample was analyzed. If Sp_{O_2} persisted at <90%, supplementary oxygen was provided by face mask to provide Sp_{O_2} > 90%. The TTS system was removed if RR was <8 breaths/min × 3 episodes/h for 2 consecutive h and/or Sp_{O_2} was <90% and Pa_{CO_2} was >55 mmHg. Removal of the TTS patches terminated the study for that patient. Respiratory monitoring, however, was continued for a further 12 h because of the fentanyl depot that develops intradermally with the TTS system and continues to maintain a plasma fentanyl concentration.[2] In the event of severe respiratory depression, naloxone was administered as required.

Adverse Effects. Nausea and vomiting were treated as needed with 25–50 mg intravenous diphenhydramine and/or 1 mg intravenous droperidol. Pruritus was treated with 50 mg intravenous diphenhydramine as needed. TTS attachment sites were assessed at regular intervals and at the time of removal for skin reactions.

Table 1. Patient Withdrawal: Respiratory Depression

Group	Age (yr)	Weight (kg)	Removal TTS (h)	Morphine (mg)	Plasma Fentanyl (ng/ml)	Naloxone (mg)	Pa_{CO_2} (mmHg)
TTSF-50	45	64	10	47	1.35	0.05	56
TTSF-50	50	60	7	4	2.19	0	56
TTSF-50	57	63	16	23	1.64	0.1	58
TTSF-75	37	66	32	19	2.23	0	51
TTSF-75	52	59	6	14	1.90	0	N/A
TTSF-75	52	72	5	16	N/A	0.04	58
TTSF-75	42	70	11	36	0.93	0	56
TTSF-75	37	51	7	10	1.10	0.2	60
TTSF-75	45	54	9	22	1.58	0.51	59

Removal TTS (h) = duration of TTS-patch before removal and withdrawal from study; Morphine (mg) = total dose of supplemental morphine before withdrawal from study; Plasma Fentanyl (ng/ml) = plasma fentanyl concentration at time of withdrawal; Naloxone (mg) = total dose of naloxone administered; Pa_{CO_2} (mmHg) = arterial P_{CO_2} at time of withdrawal; TTSF-50 = TTS-fentanyl 50; TTS-75 = TTS-fentanyl 75; N/A = no blood sample.

Data Analysis

Data are summarized as their mean value ± SEM (for parametric data) and as frequencies or percentages (for nonparametric variables) and were analyzed using one-way analysis of variance (ANOVA, *e.g.*, demographic data) or chi-squared tests of significance, respectively. Data amenable to repeated-measures ANOVA (pain intensity at rest, pain intensity with movement, supplementary morphine, vital signs) were analyzed over time (in 4- or 12-h blocks) using treatment group and study site as factors, followed by linear contrasts or Tukey's test to compare pairwise differences when the overall ANOVA was significant. Overall apnea rate and SRR/h were analyzed using a one-way ANOVA for the entire 84-h period and again between 5 and 36 h postoperatively. When the overall ANOVA demonstrated a significant group effect, Tukey's test was used for pairwise comparisons between the groups. Nonparametric data were analyzed using chi-squared, with study site as stratum, or Fisher's exact test, when necessary. The strength of the linear relationship between plasma fentanyl concentration and respiratory parameters (mean RR, SRR/h, apnea rate) was evaluated by computing Pearson product moment correlation coefficients (r) for each group every 4 h after surgery. A simple comparison of average plasma fentanyl concentration across two periods, 28–48 and 52–72 h, was made for each dosing group, using the paired t test. $P < 0.05$ was considered statistically significant for all tests.

Results

Patient Withdrawals

One hundred twenty patients were enrolled in the study, with 103 patients completing the study. Seventeen patients were withdrawn for the following reasons: Two patients did not undergo scheduled surgery, and the TTS patches were removed within 6 h of application with no adverse effects. One patient received 10 times the protocol dose of sufentanil intraoperatively and subsequently required removal of the TTS patch (3 h after application) and multiple doses of naloxone because of respiratory depression. Of the remaining 14 patients, 2 were withdrawn because of failure of respiratory monitoring equipment, 1 patient became frustrated with the respiratory monitoring regime and withdrew, 1 patient removed her patches 29 h after application, 1 patient developed pneumonia and was withdrawn, and 9 patients were withdrawn from the study because of respiratory depression (table 1). Six of the nine patients withdrawn because of respiratory depression were in the TTSF-75 group. The data from these 14 patients were included in all analyses up to the times at which they were withdrawn.

Demographic and Clinical Data

There were no significant differences between the three groups with respect to age (33–36 yr), weight (61–64 kg), duration of anesthesia (112–115 min), or duration of PACU observation period (169–184 min).

Postoperative Pain

Overall, VAS pain scores were significantly less for the TTSF-75 group at rest ($P = 0.03$) and with movement ($P = 0.04$) compared with the placebo group, but the TTSF-50 group did not differ significantly from the placebo group for either rest or movement pain. VAS pain scores were high in the early postoperative

period for all three groups (fig. 1). There was no significant difference between VAS pain scores at rest or with movement *within* each of the three groups.

Postoperative Morphine Consumption

PACU. The mean total observer-administered morphine requirements in the PACU was significantly less ($P = 0.04$) in the TTSF-75 group compared with the placebo group (TTSF-75 17.0 ± 1.4 mg, TTSF-50 18.4 ± 1.4 mg, placebo 21.9 ± 1.7 mg). Although the TTSF groups required less supplemental morphine *per hour* in the PACU than did the placebo group, this difference was only significant for the TTSF-75 group during the 3rd hour in the PACU (fig. 2).

Ward. The mean total PCA morphine requirements on the ward were significantly less for both TTSF groups (TTSF-75 39.2 ± 7.1 mg, TTSF-50 42.6 ± 6.4 mg, placebo 72.5 ± 6.9 mg; $P = 0.001$, TTSF-75, TTSF-50 *vs.* placebo). Similarly, the total postoperative supplemental morphine requirements (PACU + ward) were significantly less for the TTSF groups compared with placebo (TTSF-75 56.7 ± 7.9 mg, TTSF-50 61.2 ± 6.7 mg, placebo 94.4 ± 7.7 mg; $P = 0.0008$, TTSF-75, TTSF-50 *vs.* placebo). Between 8 and 48 h postoperatively the TTSF groups used significantly less morphine than the placebo group (fig. 2).

Respiratory Monitoring

There was no difference in the mean hourly apnea rate or in the mean number of episodes of SRR/h among

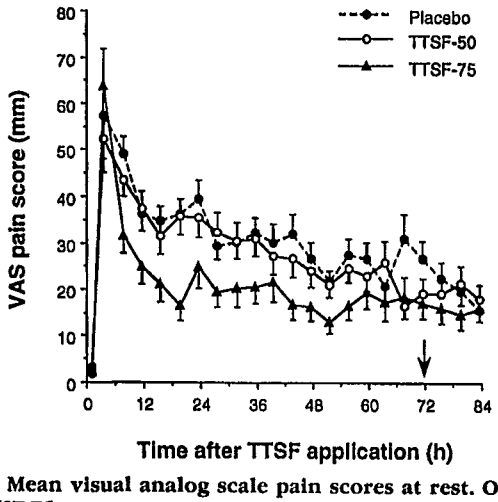

Fig. 1. Mean visual analog scale pain scores at rest. Overall, the TTSF-75 group scores were significantly lower than those in the placebo group, but the TTSF-50 group scores did not differ from the placebo group scores. The downward-pointing arrow indicates removal of the TTSF patch.

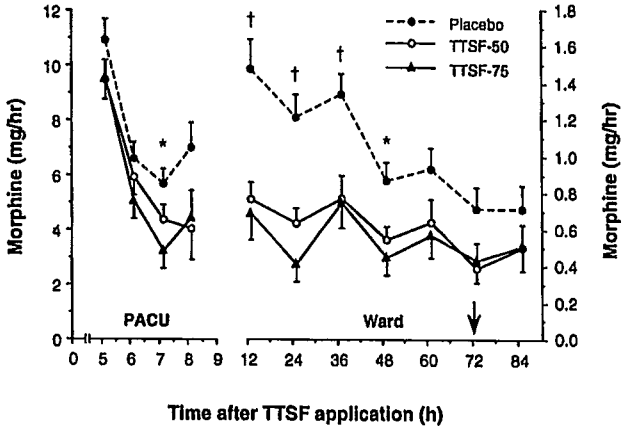

Fig. 2. Mean patient-controlled (PCA) morphine consumption in the postanesthesia care unit (PACU) and on the ward. The downward-pointing arrow indicates removal of the TTSF patch. *$P < 0.05$, placebo *versus* TTSF-75. †$P < 0.05$, placebo *versus* TTSF-50 and TTSF-75.

the groups for the 8-h preoperative monitoring period (figs. 3 and 4). However, the apnea rate between 5 and 36 h after patch application was significantly higher for TTSF-75 group compared with the placebo group but not when compared with the TTSF-50 group ($P = 0.006$; fig. 3). In addition, within this period, the three groups differed significantly in the number of patients with mean hourly apnea rate of <1 or >10 ($P < 0.006$). Only 2 patients in the placebo group had a mean hourly apnea rate of >10, whereas 28 patients had a mean hourly apnea rate of <1. In contrast, 12 patients in the TTSF-75 group had a mean hourly apnea rate of >10, and 17 patients had a mean hourly apnea rate of <1. Twenty-one patients in the TTSF-50 group had a mean hourly apnea rate of <1, and 6 had a mean hourly apnea rate of >10. Similarly, there was a significant difference between the TTSF-75 and TTSF-50 groups compared with placebo in the mean hourly number of episodes of SRR between 5 and 36 h ($P = 0.005$; fig. 4). Significantly more patients in the TTSF-75 group had a mean of 3 or more SRR episodes/h (placebo n = 5, TTSF-75 n = 22; $P = 0.003$). Sixteen patients in the TTSF-50 group had a mean of 3 or more episodes of SRR/h.

The number of patients requiring supplementary oxygen according to study criteria was significantly different for the three groups ($P < 0.001$; fig. 5). Significantly more patients in the TTSF-75 group (n = 25) received oxygen supplementation when compared with the TTSF-50 (n = 12) and the placebo group (n = 7).

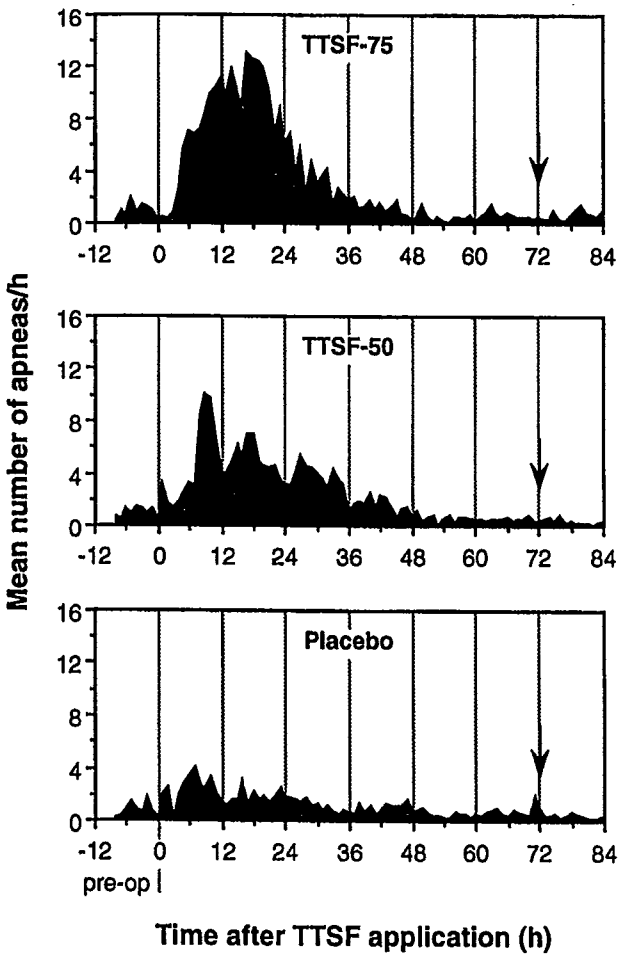

Fig. 3. Mean apnea/h (apnea = 15 s + Vt < 100 ml). Between 5 and 36 h, mean apnea/h in the TTSF-75 group was higher than in the placebo group ($P < 0.006$). The downward-pointing arrow indicates removal of the TTSF patch.

Oxygen supplementation was not necessary after 48 h (fig. 5). Significantly more patients in the TTSF groups required arterial blood gas sampling compared with the placebo group (placebo n = 12, TTSF-50 n = 24, TTSF-75 n = 25; $P = 0.04$), and mean Pa_{CO_2} was significantly different in the TTSF-75 group compared with placebo (TTSF-75 $Pa_{CO_2} = 47 \pm 1$, placebo $Pa_{CO_2} = 42 \pm 1$; $P = 0.04$). There were no patient withdrawals due to adverse respiratory events in the placebo group, but three and six patients were withdrawn from the TTSF-50 and TTSF-75 groups, respectively, because of severe respiratory depression. Patient withdrawals for severe respiratory depression in the TTSF groups occurred within 5–32 h after patch application (table 1). Naloxone for respiratory depression reversal was not required for any patient in the placebo group, whereas two patients in the TTSF-50 and three patients in the TTSF-75 group were treated with naloxone (table 1).

Adverse Effects

There was no significant difference in the incidence of adverse effects (nausea and/or vomiting: placebo n = 19, TTSF-50 n = 23, TTSF-75 n = 23; pruritus: placebo n = 4, TTSF-50 n = 2, TTSF-75 n = 5; $P = 0.4$).

Pharmacokinetic Analysis

Eight hundred five blood samples (TTSF-50 n = 434, TTSF-75 n = 371) were analyzed for fentanyl concen-

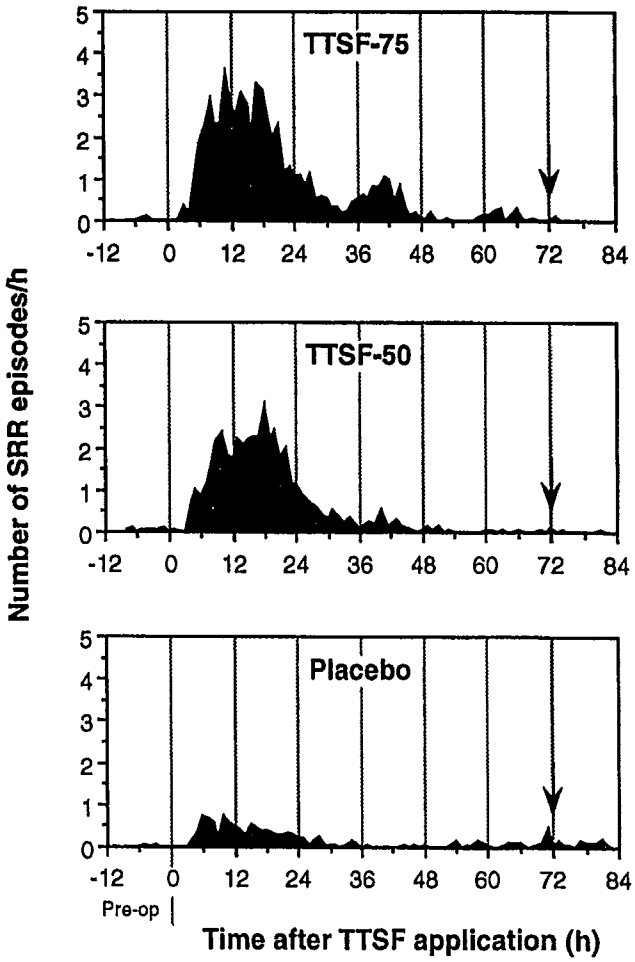

Fig. 4. Mean hourly number of 5-min episodes of slow respiratory rate (SRR, <8 breaths/min for 5 min). There were significantly more episodes of SRR/h in the TTSF-50 and TTSF-75 groups compared with the placebo group between 5 and 36 h ($P = 0.05$). The downward-pointing arrow indicates removal of the TTSF patch.

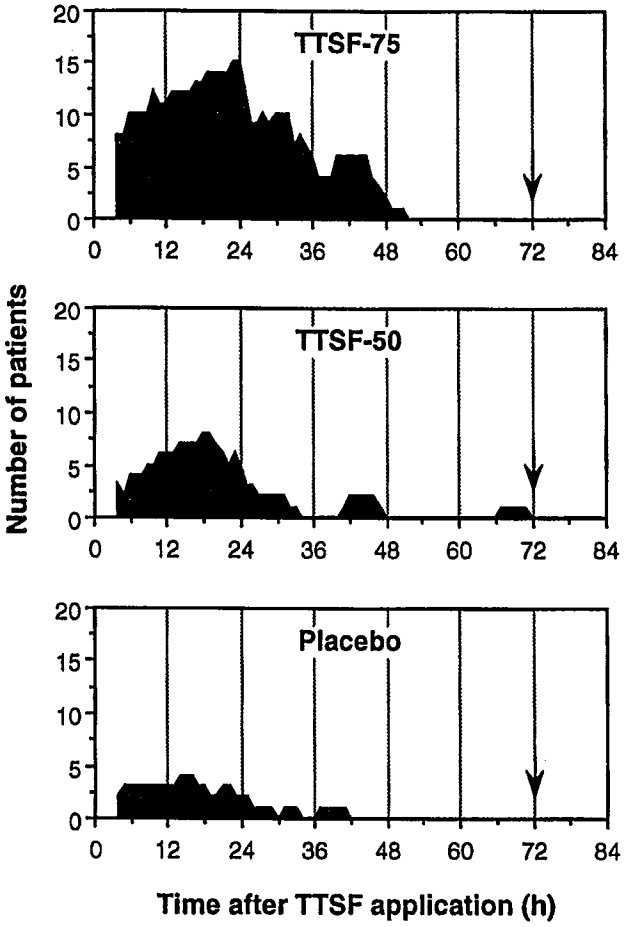

Fig. 5. Number of patients receiving supplementary oxygen in group TTSF-75 was significantly greater than the TTSF-50 or placebo groups ($P < 0.001$). Supplementary oxygen was started and arterial blood gas drawn if respiratory rate was <8 breaths/min and/or Sa_{O_2} was <90%. The downward-pointing arrow indicates removal of the TTSF patch.

tration. Plasma fentanyl concentration reached a relatively steady-state by approximately 16–20 h after patch application for both the TTSF-75 and the TTSF-50 group (fig. 6). In general, patients with the 75-μg/h patches had higher plasma fentanyl concentrations than did patients with the 50-μg/h patches, although the difference between the groups was not significant. Plasma fentanyl concentration was significantly lower during the 3rd day of patch application compared with the 2nd day for both TTSF groups (mean plasma fentanyl concentration: TTSF-50 28–48 h = 1.15 ± 0.11 ng/ml, 52–72 h = 0.77 ± 0.09 ng/ml ($P = 0.0001$); TTSF-75 28–48 h = 1.56 ± 0.20 ng/ml, 52–72 h = 1.06 ± 0.11 ng/ml ($P = 0.004$)). The change in mean plasma fentanyl concentration represents a 33% decrease from the mean plasma fentanyl concentration on the 2nd day. Area under the curve, 0–84 h (trapezoidal rule, mean data) for TTSF-75 was 103.8 $ng \cdot h \cdot ml^{-1}$ and for TTSF-50 was 76.1 $ng \cdot h \cdot ml^{-1}$. The ratio of area under the curve, TTSF-75:TTSF-50, is 1.4.

Figure 7 shows the correlation coefficients between plasma fentanyl concentration and mean RR, SRR/h, and mean hourly apnea rate for the TTSF-75 and TTSF-50 groups on a 4-hourly basis after surgery. With the exception of a few time points, there was no significant linear relationship between plasma fentanyl concentration and respiratory parameters. When Bonferroni's type 1 error rate correction for multiple correlation coefficients (*i.e.*, $\alpha = 0.05$/number of tests) was used, no correlation coefficient reached statistical significance. These graphs indicate that, when data from all patients are used, there is no tendency for plasma fentanyl concentration to be significantly correlated with the three respiratory parameters.

Discussion

This study demonstrated that the TTSF patch (50–75 μg/h) provides dose- and time-dependent analgesic efficacy to patients undergoing abdominal hysterectomy. As in other studies, we found a reduced ongoing need for PCA supplementation in the TTSF groups. However,

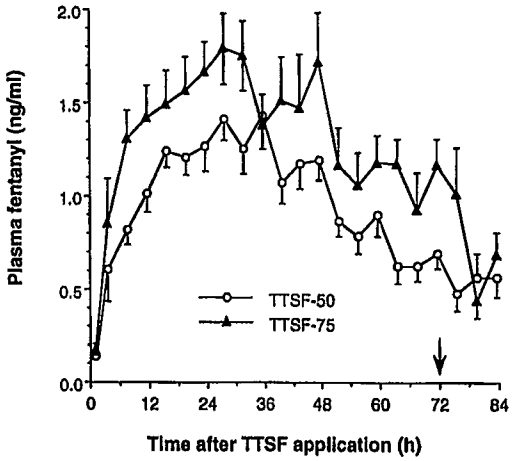

Fig. 6. Plasma fentanyl concentration by radioimmunoassay method. Mean plasma fentanyl concentration between 52 and 72 h was significantly lower than the mean plasma fentanyl concentration between 28 and 48 h for both TTSF groups. The downward-pointing arrow indicates removal of the TTSF patch.

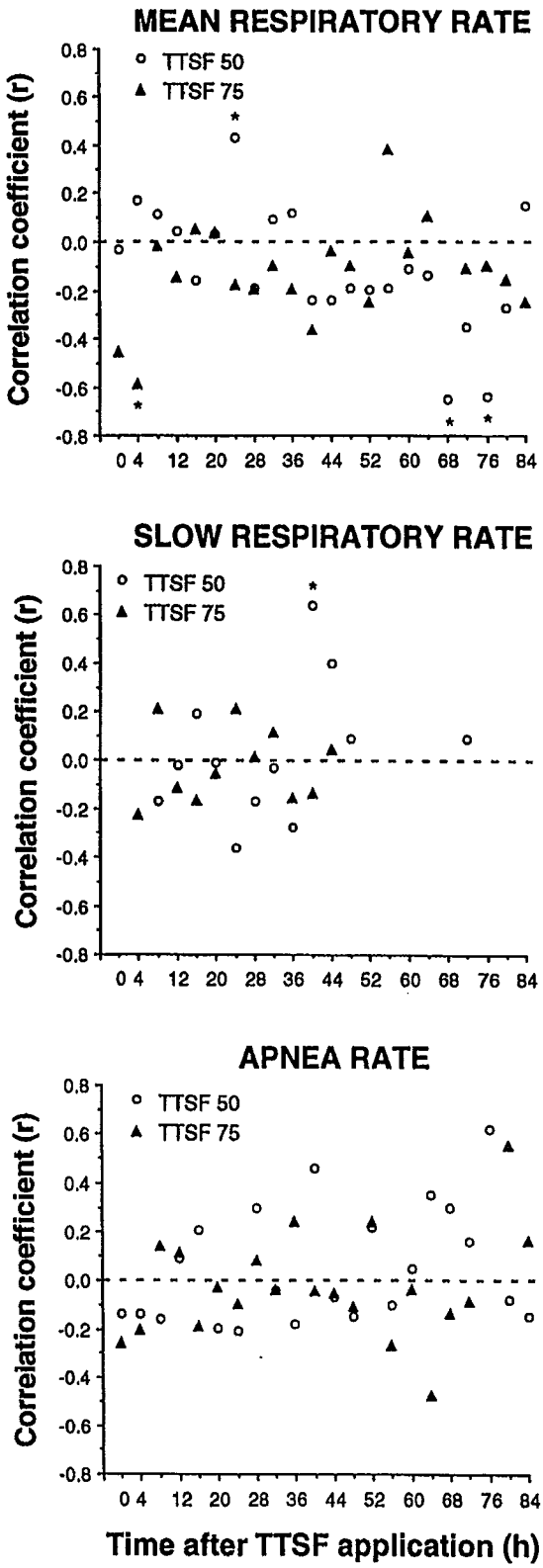

Fig. 7. Pearson product-moment correlation coefficients (r) between plasma fentanyl concentration and the three respiratory parameters for the TTSF-50 and TTSF-75 groups every 4 h after surgery. Each point represents the correlation coefficient between plasma fentanyl concentration and one of the three respiratory parameters at a given time after surgery. *$P < 0.05$. (Note: Using Bonferroni type 1 error rate correction for multiple tests of significance, none of the correlation coefficients reached statistical significance.)

the respiratory depression observed was of a significant degree and gave rise to concern about patient welfare, in contrast to observations made with PCA alone.

The TTSF patch is a slow-onset, easy-to-use, noninvasive transdermal infusion device that produces plasma concentrations similar to those achieved with an intravenous infusion of fentanyl.[2,3] The plasma concentration of fentanyl will be related to the degree of analgesia produced and the production of adverse effects, but in individual patients, analgesia and other opioid effects are modified by other factors, such as age, individual sensitivity, concomitant medications or other interventions, and underlying disease states. Fentanyl, like all opioids, has a relatively restricted clinically useful dose-response range that can be defined as the range between the minimally effective analgesic concentration (MEAC) and the highest tolerable analgesic concentration before the production of significant respiratory depression.[20] Several studies using PCA or fentanyl infusions showed the MEAC for fentanyl to vary between 0.6 and 1.7 ng/ml.[18,21–25] Individual patients, however, will vary in MEAC requirements over as much as a sixfold range.[24,26] Clinically significant respiratory depression was measured in similar studies with plasma fentanyl concentrations of 1–3 ng/ml.[2,27–29]

Pharmacokinetic Analysis

The peak plasma concentrations produced by TTSF-50 and TTSF-75 patches in this study are similar to those described in other TTSF patch studies.[3,4,6–8,11,13,30] This report is the first large study to report pharmacokinetic data with a TTSF patch in place for 72 h. Mean fentanyl plasma concentration is significantly lower on the 3rd day (52–72 h) compared with the 2nd day (28–48 h) for both TTSF groups, indicating that both the 50-μg/h and the 75-μg/h patch did not provide steady-state plasma fentanyl concentration after 2 days of application. In the current study, although *mean* plasma fentanyl concentration was within the therapeutic range between 14 and 48 h after patch application, most patients in the TTSF

groups required PCA morphine supplementation for satisfactory analgesia.

Postoperative Analgesia and Morphine Supplementation

A clear disadvantage of the TTSF system is the slow development of effective plasma concentration. Thus, in this study in which the TTSF patches were applied 2 h preoperatively and only modest doses of intraoperative opioid were administered, high pain scores and high morphine requirements were seen in the immediate postoperative period in the PACU for all three groups (figs. 1 and 2). At 12 h postoperatively, PCA morphine requirements for the TTSF groups were markedly decreased, reflecting fentanyl plasma concentration approaching analgesic concentrations. The placebo group (PCA only) maintained greater morphine requirements for the full 84 h. In addition, the placebo group characteristically did not achieve VAS scores less than 30% of maximum VAS. This finding is similar to what other studies found when patients use PCA.[31,32] Other investigators reported similar findings to those found in this study, *i.e.,* lower VAS scores (especially in those studies using 50–100-μg/h TTSF patches)[4,5,12,14,15] and lower opioid supplementation in the TTSF groups.[4,5,12,14,15,33] It is significant to note that the majority of the subjects in these studies and in ours required opioid supplementation despite the application of a TTSF patch.[14]

Respiratory Effects

The rationale for the use of noninvasive continuous electronic monitoring systems to measure respiratory pattern and pulse oximetry in postoperative analgesic studies was documented elsewhere[34] and validated in studies from our group and others.[14,17,18,35,36] In general, the system provides a nondisturbing mechanism of observing and recording clinically significant respiratory depression in the clinical setting.[37] The use of a nondisturbing system to measure respiratory pattern and hypoxemia allows study of the postoperative patient in a setting as close to real life as possible. Other useful techniques to measure opioid-induced respiratory depression, such as carbon dioxide-response tests, produce alertness and arousal that alter the conditions normally found in the postoperative patient. Catley *et al.*[36] showed correlation between changes in ventilatory pattern and episodic oxygen desaturation when opioid analgesics are used postoperatively, thus demonstrating noninvasive monitoring techniques to be useful indicators of respiratory risk. In this study, we observed a dose-dependent increase in the apnea rate and episodes of SRR/h for each group as the dose of TTSF was increased (figs. 3 and 4). In addition, the number of patients with significant apnea rates, SRR episodes, and hypoxemia (*i.e.,* requiring supplementary oxygen) increased significantly as the dose of TTSF was increased (fig. 5). Similarly, the number of patients requiring arterial blood gas analysis (on the basis of the criteria outlined above) was significantly greater among patients in the TTSF groups. The development of carbon dioxide retention increased as the dose of TTSF was increased (table 1). None of the patients in the three groups had evidence of sleep apnea or respiratory pattern abnormalities from the preoperative monitoring results. It was significant that 9 of 80 (11.3%) of the patients in the TTSF groups were withdrawn because of increasingly severe respiratory depression. On the basis of the findings in this study and in others,[17,18,35–37] noninvasive monitoring systems of respiratory function, when coupled with pulse oximetry, provide as good an indicator of risk of respiratory depression in the clinical setting as is currently possible.[34]

Respiratory depression following the use of the TTSF patch has not been examined systematically. Several investigators reported a low incidence of moderate to severe respiratory depression in previous studies.[4,5,7,10,11,13,14,38] Respiratory depression was defined as RR < 8–10 breaths/min for the majority of these studies, and RR was measured intermittently. Exclusion of continuous monitoring, especially hemoglobin saturation, in these studies (table 2) may lead to underestimation of the incidence of clinically significant respiratory depression. However, even in these earlier studies, an incidence of respiratory depression, as defined by the authors, of approximately 10% was seen in many of them in the groups receiving transdermal fentanyl (table 2). A significant feature of the current findings was the relative restriction of respiratory depression to the 5–36-h period postoperatively. The occurrence of respiratory depression within this period corresponds with reports of other investigators.[4,5,7,10,11,14,38] The mechanism of the respiratory depression in the current study probably is related to the slow development of analgesic plasma concentrations of fentanyl with the TTSF system and the requirement for larger doses of morphine in the PACU to control early postoperative pain. The additive effects of the two opioids and the continuing PCA morphine requirements are the most probable reason for the dose-

Table 2. Transdermal Fentanyl: Comparative Studies—Respiratory Depression

Study	Incidence		Description	Treatment
	Active (Size)	Placebo		
Bormann (1988)[5]	1/20 (75)	0/20	SRR (ward)	1 patient: naloxone, TTS removed
Duthie (1988)[13]	2/9 (100)	—	SRR (ward)	TTS removed
Gourlay (1989)[11]	3/13 (50–125)	—	SRR (ward)	1 patient: naloxone; 2 patients: oxygen (mask)
Caplan (1989)[4]	3/22 (75)	0/20	SRR (ward)	Patients aroused
Latasch (1989)[7]	1/30 (75)	0/30	Hypoxia/hypercapnia	No treatment
Boerner (1991)[38]	2/12 (60)	0/12	Not described	Unknown treatment
Sevarino (1992)[10]	2/32 (25), 3/32 (50)	0/32	SRR (PACU)	1 patient: naloxone
Sandler (1994)	3/37 (50), 6/39 (75)	0/36	AP (PACU/ward), SRR (PACU/ward), hypoxia/hypercapnia	TTS removed, oxygen (mask) (2/TTS-50), naloxone (3/TTS-75), naloxone

Incidence = number of patients with clinically significant respiratory depression in each group; Active = TTS-fentanyl group; Size = TTS-fentanyl patch size; Placebo = placebo TTS group; treatment = treatment for respiratory depression; SRR = slow respiratory rate; ward = abnormal respiratory pattern on ward; PACU = abnormal respiratory pattern in postanesthesia care unit; AP = apneic episodes.

related increase in respiratory abnormalities and increased requirement for oxygen supplementation seen in the TTSF groups up to 36 h postoperatively. The decrease in respiratory depression after 36–48 h probably is related to the decrease in plasma fentanyl concentration at this time (fig. 6). An analysis of pharmacodynamic relationships between plasma fentanyl concentration and mean RR, SRR, and apnea revealed no correlation between any of the three respiratory parameters and plasma fentanyl concentration at any time when blood was sampled for plasma fentanyl (fig. 7). This indicates the high degree of variability in the occurrence of respiratory depression in the clinical setting due to factors discussed above and the difficulty in assigning a plasma fentanyl concentration at which respiratory depression occurs in the individual patient. Thus, it is possible that, in the postoperative period, for the individual patient, there may be as large a variability in plasma fentanyl concentration producing clinically significant respiratory depression as there is for the MEAC.[24,26] This study also documented the relative safety of PCA morphine alone (placebo group) in terms of respiratory pattern and postoperative hypoxemia, although minimal alterations in these parameters were present secondary to postsurgical and anesthetic effects.[39,40] The incidence of severe respiratory depression when opioids are administered by other routes is much less than the 11% incidence found in the current study. For example, the incidence of respiratory depression with intramuscular administration of opioids is approximately 0.9%[41] and for spinal opioid administration is 0.2–0.36%.[42] In a large retrospective study, the incidence of severe respiratory depression in patients using PCA was 0.5%.[43]

Most investigators found that the TTSF patch requires analgesic supplementation to provide effective pain relief, and the majority of studies used opioids as the supplementary analgesic agent. However, in the one study to date that used a nonsteroidal antiinflammatory drug as the supplementary analgesic agent, the incidence of respiratory depression ($\uparrow Pa_{CO_2}$, $\downarrow$RR) was low despite the use of a 75-μg/h TTSF patch.[7] Similarly, in another study using the TTSF-75 patch in 50 patients, no clinically significant respiratory depression ($\downarrow$RR) was recorded when fentanyl was used as the supplementary analgesic.[44] Both of these studies had the patch applied for 24 h only, and therefore, serum fentanyl concentration would have decreased after 24 h and would not summate with supplementary analgesic therapy to produce respiratory depression.

In contrast to early reports[4,8,9,13] that hailed the TTSF patch as a major analgesic breakthrough for acute pain management, we conclude that the high incidence of respiratory depression under the conditions of the current study requires the TTSF system to be used only under closely monitored conditions for acute postoperative pain with resuscitation facilities close at hand. This applies to the small number of patients who will be able to use the TTSF patch as a sole analgesic system but will be particularly applicable if opioid or sedative supplementation is necessary. Thus, we do not recommend the routine use of the TTSF patch for acute pain control unless the above stipulations are met. Nevertheless, the TTSF system has several major advan-

tages (*e.g.*, ease of use, high patient acceptability, increased analgesic effectiveness, nonlabor-intensive) that warrant further study to characterize other possible uses. Investigation into the use of the TTSF patch as a component of a multimodal analgesic system (*i.e.*, in conjunction with an α agonist and a nonsteroidal antiinflammatory drug) may provide an effective postoperative analgesic regimen. In addition, in the treatment of chronic cancer pain, the advantages of the TTSF patch combined with the system's sustained drug release profile make it useful. This is evidenced by the fact that TTSF is used as a highly effective analgesic for chronic cancer pain and is approved for this use in several countries.

References

1. Nairn JG: Transdermal therapeutic systems: Some fundamental considerations. Can J Hosp Pharm 41:85–88, 1988
2. Hill HF: Clinical pharmacology of transdermal fentanyl. Eur J Pain 11:81–91, 1990
3. Varvel JR, Shafer SL, Hwang SS, Coen PA, Stanski DR: Absorption characteristics of transdermally administered fentanyl. ANESTHESIOLOGY 70:928–934, 1989
4. Caplan RA, Ready LB, Oden RV, Matsen FA, Nessly ML, Olsson GL: Transdermal fentanyl for postoperative pain management: A double-blind placebo study. JAMA 261:1036–1039, 1989
5. Bormann BV, Ratthey K, Schwetlick G, Schneider C, Muller H, Hempelmann G: Postoperative schmerztherapie durch transdermales fentanyl. Anasth Intensivther Notfallmed 23:3–8, 1988
6. Holley FO, Van Stennis C: Postoperative analgesia with fentanyl: Pharmacokinetics and pharmacodynamics of constant-rate iv and transdermal delivery. Br J Anaesth 60:608–613, 1988
7. Latasch L, Luders S: Transdermal fentanyl against postoperative pain. Acta Anaesthesiol Belg 40:113–119, 1989
8. Plezia PM, Kramer TH, Linford J, Hameroff SR: Transdermal fentanyl: Pharmacokinetics and preliminary clinical evaluation. Pharmacotherapy 9:2–9, 1989
9. Lehmann KA, Einnolf C, Eberlein HJ, Nagel R: Transdermal fentanyl for the treatment of pain after major urological operations. Eur J Clin Pharmacol 41:17–21, 1991
10. Sevarino FB, Naulty JS, Sinatra R, Chin ML, Paige D, Conry K, Silverman DG: Transdermal fentanyl for postoperative pain management in patients recovering from abdominal gynecologic surgery. ANESTHESIOLOGY 77:463–466, 1992
11. Gourlay GK, Kowalski SR, Plummer JL, Cherry DA, Gaukroger P, Cousins MJ: The transdermal administration of fentanyl in the treatment of postoperative pain: Pharmacokinetics and pharmacodynamic effects. Pain 37:193–202, 1989
12. Rowbotham DJ, Wyld R, Peacock JE, Duthie DJR, Nimmo WS: Transdermal fentanyl for the relief of pain after abdominal surgery. Br J Anaesth 63:56–59, 1989
13. Duthie DJR, Rowbotham DJ, Wyld R, Henderson PD, Nimmo WS: Plasma fentanyl concentrations during transdermal delivery of fentanyl to surgical patients. Br J Anaesth 60:614–618, 1988
14. Sandler A: Transdermal fentanyl: Acute analgesic studies. J Pain Symptom Management 7:S27–S35, 1992
15. McLesky CH: Fentanyl TTS for postoperative analgesia. Eur J Pain 11:92–97, 1990
16. Sackner MA, Watson H, Belsito AS, Feinerman D, Suarez M, Gonzalez G, Bizousky F, Krieger B: Calibration of respiratory inductive plethysmograph during normal breathing. J Appl Physiol 66:410–420, 1989
17. Sandler AN, Chovaz P, Whiting W: Respiratory depression following epidural morphine: A clinical study. Can Anaesth Soc J 33: 542–549, 1986
18. Sandler AN, Stringer D, Panos L, Badner N, Friedlander M, Koren G, Katz J, Klein J: A randomized, double-blind comparison of lumbar epidural and intravenous fentanyl infusions for postthoracotomy pain relief. ANESTHESIOLOGY 77:626–634, 1992
19. Michiels M, Hendricks R, Heykants J: A sensitive radioimmunoassay for fentanyl. Eur J Clin Pharmacol 12:153–158, 1977
20. Mather LE, Owen H: The scientific basis of patient-controlled analgesia. Anaesth Intensive Care 16:427–447, 1988
21. Nimmo WS, Todd JG: Fentanyl by constant rate i.v. infusion for postoperative analgesia. Br J Anaesth 57:250–254, 1985
22. Lehmann KA: Practical experience with demand analgesia for postoperative pain, Patient-Controlled Analgesia. Edited by Harmer M, Rosen M, Vickers MD. Oxford, Blackwell Scientific, 1985, pp 134–139
23. Hackl W, Fitzal S, Lackner F, Weindlmayr-Goettel M: Vergleich von Fentanyl und Tramadol zur Schmerzbehandlung mittels on-demand-analgesie-Computer in der frühen potoperativen Phase. Anaesthestist 35:317–319, 1986
24. Gourlay GK, Kowalski SR, Plummer JL, Cousins MJ, Armstrong PJ: Fentanyl blood concentration-analgesic response relationship in the treatment of postoperative pain. Anesth Analg 67:329–337, 1988
25. Duthie DJR, McLaren AD, Nimmo WS: Pharmacokinetics of fentanyl during constant rate iv infusion for the relief of pain after surgery. Br J Anaesth 58:950–956, 1986
26. Lehmann KA, Heinrich C, van Heiss R: Balanced anaesthesia and patient-controlled postoperative analgesia with fentanyl: Minimum effective concentrations, accumulation and acute tolerance. Acta Anaesth Belg 39:11–23, 1988
27. Cartwright P, Prys-Roberts C, Gill K, Dye A, Stafford M, Gray A: Ventilatory depression related to plasma fentanyl concentrations during and after anesthesia in humans. Anesth Analg 62:966–974, 1983
28. Andrews CJH, Sinclair M, Prys-Roberts C, Dye A: Ventilatory effects during and after continuous infusions of fentanyl or alfentanil. Br J Anaesth 55:211S–216S, 1983
29. Hill HF, Chapman CR, Saeger L, Bjurstrom R, Walter MH, Kippes M: Steady-state infusions of opioids in humans: II. Concentration-effect relationships and therapeutic margins. Pain 43:69–79, 1990
30. Esteve M, Levron JC, Flaisler B, Schoefler P, Duvaldestin P, Chauvin M: Does aging modify pharmacokinetics of transdermal fentanyl (abstract)? ANESTHESIOLOGY 75:A705, 1991
31. Eisenach JC, Grice SC, Dewan DM: Patient-controlled analgesia following cesarean section: A comparison with epidural and intramuscular narcotics. ANESTHESIOLOGY 68:444–448, 1988
32. Ferrante FM, Orav EJ, Rocco AG, Gallo J: A statistical model for pain in patient-controlled analgesia and conventional intramuscular opioid regimens. Anesth Analg 67:457–461, 1988
33. Gourlay GK, Kowalski SR, Plummer DA, Szekely SM, Mather LF, Owen H, Cousins MJ: The efficacy of transdermal fentanyl in the treatment of postoperative pain: A double-blind comparison of fentanyl and placebo systems. Pain 40:21–28, 1990

34. Sandler AN: Opioid-induced respiratory depression in the postoperative period, Management of Postoperative Pain, Anesthesiology Clinics of North America. Edited by Oden RV. Philadelphia, WB Saunders 1989, pp 193–210

35. Catling JA, Pinto DM, Jordan C: Respiratory effects of analgesia after cholecystectomy: Comparison of continuous and intermittent papaveretum. Br Med J 281:478–480, 1980

36. Catley DM, Thornton C, Jordan C, Lehane JR, Royston D, Jones JG: Pronounced episodic oxygen desaturation in the postoperative period: Its association with ventilatory pattern and analgesic regimen. ANESTHESIOLOGY 63:20–28, 1985

37. Jordan C: Assessment of the effects of drugs on respiration. Br J Anaesth 54:763–782, 1982

38. Boerner TF, Bell S, Bartkowski R, Torjman M, Lessin J, Marr A: Transdermal fentanyl delivery system vs morphine IM: A comparison of analgesia after major orthopedic surgery (abstract). ANESTHESIOLOGY 75:A709, 1991

39. Craig DB: Postoperative recovery of pulmonary function. Anesth Analg 60:46–52, 1981

40. Marshall BE, Wyche MQ Jr: Hypoxemia during and after anesthesia. ANESTHESIOLOGY 37:178–209, 1972

41. Miller RR: Analgesics, Drug Effects in Hospitalized Patients. Edited by Miller RR, Greenblatt DJ. New York, John Wiley & Sons, 1976, pp 133–164

42. Etches RC, Sandler AN, Daley MD: Respiratory depression and spinal opioids. Can J Anaesth 36:165–185, 1989

43. Etches RC: Respiratory depression associated with patient-controlled analgesia: A review of eight cases. Can J Anaesth 41:125–132, 1994

44. Lehmann KA, Einnolf C, Eberlein HJ, Nagel R: Transdermal fentanyl for the treatment of pain after major urological operations: A randomized double-blind comparison with placebo using intravenous patient-controlled analgesia. Eur J Clin Pharmacol 41:17–21, 1991