The effect of rectal temperature on perianesthetic serum concentrations of transdermally administered fentanyl in cats anesthetized with isoflurane

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Objectives—To determine whether moderate hypothermia during 4 hours of anesthesia with isoflurane substantially affects serum concentrations of transdermally administered fentanyl in the perianesthetic period in cats.

Animals—7 healthy mature cats.

Procedure—A fentanyl patch (25 µg/h) was applied to the shaved thorax 24 hours before induction of anesthesia. Anesthesia was induced at time 0. Each cat received 2 treatments in a random order. Treatments were isoflurane anesthesia with normothermia and isoflurane anesthesia with hypothermia. Cats were intubated, connected to a nonrebreathing circuit, and maintained at 1.3X minimum alveolar concentration for 4 hours. Cats in the hypothermia treatment groups were actively cooled to 35°C following the induction of anesthesia. Serum fentanyl analysis was performed at –24, –12, 0, 1, 2, 3, 4, 4.5, 5, 6, 7, 8, 9, 10, 12, and 24 hours.

Results—Mean ± SEM serum fentanyl concentration (SFC) for the hypothermia treatment group (0.598 ± 0.3048 ng/mL) was significantly lower than the baseline concentration (1.834 ± 0.6393 ng/mL) at 1 hour. This significant reduction persisted for the duration of anesthesia for the hypothermia treatment group. Serum fentanyl concentrations returned to baseline values within 1 hour of the end of anesthesia, regardless of body temperature.

Conclusions and Clinical Relevance—Hypothermia during inhalant anesthesia induced a significant reduction in SFC obtained with transdermal administration. The impact of this reduction in SFC on the contribution of transdermally administered fentanyl to any reduction in the need for inhalant anesthesia remains to be determined. (*Am J Vet Res* 2003; 64:1557–1561)

Transdermal administration of fentanyl citrate has been reported in cats,[1,2] dogs,[3-5] sheep,[a] horses,[b] rabbits,[6] goats,[7] and pigs.[8,9] Transdermal administration of fentanyl to cats significantly reduces the **minimum alveolar concentration (MAC)** of isoflurane, decreasing the need for inhalant anesthesia.[10] In addition, the use of transdermally administered fentanyl is effective in relieving pain associated with ovariohysterectomy and onychectomy.[1,11]

Despite the frequent use of transdermal fentanyl in animals undergoing anesthesia with or without surgery, little is known about how anesthesia and surgery affect the performance of the delivery system. Dogs undergoing surgery have higher mean plasma fentanyl concentrations, compared with controls that receive neither anesthesia nor surgery, suggesting that surgery or anesthesia may cause variability in **serum fentanyl concentrations (SFCs)** during transdermal administration.[3] A more recent study[c] in dogs has confirmed that hypothermia induces significant reductions in SFC in anesthetized dogs during the anesthetic period and that these reductions are more protracted with isoflurane anesthesia. How these reductions in SFC during anesthesia and hypothermia influence intraoperative analgesia has not been assessed.

In cats undergoing ovariohysterectomy, there are no significant differences in pre- and postoperative SFC during transdermal administration, compared with cats receiving transdermal fentanyl without anesthesia or surgery.[2] Yackey et al[10] reported that the highest SFCs during transdermal administration during a 144-hour period were achieved during MAC determinations and isoflurane anesthesia. Although this observation suggests variability in SFC during isoflurane anesthesia, the SFC profile during a prolonged period of anesthesia has not been reported. In addition, the influence of body temperature on SFC obtained with transdermal administration during isoflurane anesthesia, as reported for dogs,[c] has not been determined in cats.

The purpose of the study reported here was to determine whether moderate hypothermia during 4 hours of anesthesia with isoflurane substantially affects the serum concentrations of transdermally administered fentanyl in the perianesthetic period in cats.

Materials and Methods

Animals—This study was approved by the Institutional Animal Care and Use Committee of the Louisiana State University. Seven healthy mature domestic shorthair cats owned by the University and weighing 5.6 ± 0.44 kg (mean ± SEM; range, 4.2 to 7.8 kg) were used. Cats were confirmed to be healthy by results of a general physical examination, CBC, and serum biochemical analyses performed before the study.

Each cat received 2 treatments in a random order. The 2 treatments were **isoflurane anesthesia with normothermia (Iso-norm)** and **isoflurane anesthesia with hypothermia**

Received January 7, 2003.
Accepted April 1, 2003.
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Supported by the Pet Trust Fund, Ontario Veterinary College, University of Guelph, ON, Canada, and the Competitive Organized Research Program, School of Veterinary Medicine, Louisiana State University.
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(**Iso-hypo**). There was a minimum of 7 days between treatments for each cat.

Twenty-four hours before induction of anesthesia, a fentanyl (25 µg/h) patch[d] was applied to the lateral thorax of the cat. The initial side of the thorax chosen for patch placement was determined by coin toss. Subsequent patch placement for the second treatment was made on the opposite side. The area for patch placement was clipped free of hair, with care taken not to abrade the skin. The clipped area was brushed clean but not scrubbed. The patch was placed on the clipped area, held in place to ensure adhesion, and covered with elastic tape.[e] The elastic tape was covered with a single layer of bandaging tape.[f]

Anesthesia and instrumentation—Food was withheld from all cats for 12 hours before induction of anesthesia. Anesthetic inductions were performed at the same time each day. Anesthesia was induced by facemask with isoflurane in 100% oxygen. Following induction, the trachea was intubated with an appropriately sized endotracheal tube and cats were connected to a nonrebreathing circuit (Bain) with a fresh gas flow rate of 200 mL/kg/min. The inhaled anesthetic was delivered at 1.3X the MAC value for isoflurane in cats.[12] Cats breathed spontaneously throughout anesthesia. To simulate those situations in which mechanical positive-pressure ventilation or **end-tidal carbon dioxide** ($ETCO_2$) monitoring are not available, there was no attempt to supplement the spontaneous ventilation with positive-pressure ventilation during the anesthetic period even in the presence of bradypnea and high partial pressure of CO_2 in expired gas. Anesthesia lasted 4 hours from the time of induction.

A 20-gauge, 1.6-cm catheter was placed in a cephalic vein for the administration of a balanced electrolyte solution[g] (5 mL/kg/h) for the duration of anesthesia. Blood pressure was measured indirectly by use of an ultrasonic Doppler flow detector[h] with the flow probe placed over the cranial tibial artery distal to the tarsal-metatarsal joint. An appropriately sized pediatric inflatable blood pressure cuff attached to a sphygmomanometer was placed above the probe. A standard lead-II ECG, rectal temperature, and **oxygen saturation as measured by pulse oximetry** (SpO_2) were monitored[i] during anesthesia. Inspired and end-tidal inhalant concentrations and $ETCO_2$ were measured with a sidestream analyzer.[j]

Data collection—Heart rate (HR), **respiratory rate (RR)**, rectal temperature, $ETCO_2$, SpO_2, end-tidal inhalant concentrations, and **systolic blood pressure (SBP)** were recorded immediately following anesthesia induction and every 15 minutes for the 4 hours of anesthesia. Otherwise, in the pre- and postanesthetic periods, HR, RR, and rectal temperature were recorded in conjunction with each blood sampling.

Rectal temperature—For the Iso-norm treatment group, cats were kept warm with thermostatically controlled circulating hot-water blankets and were covered with towels. The goal in the normothermic treatment group was to maintain rectal temperature within 1°C of the temperature recorded before the induction of anesthesia. For the Iso-hypo treatment group, cats were placed on the same circulating water blankets with the thermostat set at 35°C. Following induction of anesthesia during the hypothermia treatments, cats were actively cooled to 35°C by placing towel-wrapped ice packs in the inguinal and axillary regions. The goal in the hypothermic treatment group was to maintain the rectal temperature at 35°C. In all treatments, cats were in lateral recumbency so that the side with the fentanyl patch was on the nondependent side of the cat. Care was taken to ensure that the fentanyl patch did not come in contact with the circulating water blankets or ice packs. There was no attempt to rewarm hypothermic cats in the postanesthetic period. All ice packs were removed when the target temperature was reached and replaced intermittently if required. Ice packs were removed at the end of the anesthetic period. Normothermic cats remained covered and on the circulating water blanket until they were extubated and able to maintain sternal recumbency.

Fentanyl analysis—Blood samples for analysis of fentanyl concentration were drawn at –24, –12, 0, 1, 2, 3, 4, 4.5, 5, 6, 7, 8, 10, 12, and 24 hours, where time 0 was the time of induction of anesthesia. Before the induction of anesthesia, samples were drawn from a jugular vein with a needle and syringe. During anesthesia and the postanesthetic periods, samples were drawn from an 18-gauge, 28-cm, through-the-needle catheter,[k] which had been placed in 1 jugular vein immediately following the induction of anesthesia. For each sample, 1 mL of blood was drawn, placed in a serum tube, cooled, and centrifuged to harvest the serum. Serum was stored at –70°C until the fentanyl analysis was performed by radioimmunoassay.[l]

Statistical analyses—The fentanyl concentration was considered to be continuous and determined to follow a normal distribution by use of the Shapiro-Wilk W test with failure to reject the null hypothesis of normality at $P \leq 0.05$. Data were summarized and graphed as mean ± SEM. The fentanyl concentration was evaluated for differences across time and between treatments by use of a mixed linear model that included the random variance of cat and accounted for the repeated measurements over time. Where there were significant effects of treatment and time and significant interaction of treatment and time at $P \leq 0.05$, selected comparisons within treatments over time and among treatments at various time points were made by use of least-squares means maintaining experiment-wise type-I error at 0.05. Thus, unless stated, where a difference is noted, $P \leq 0.05$.

By use of the trapezoidal method, partial area under the SFC versus time curve (AUC) from the time of anesthesia induction (t = 0) to 1 hour after the end of anesthesia (t = 5 hours; $AUC_{0\text{-}5}$) was calculated for each cat. The $AUC_{0\text{-}5}$ was evaluated for differences between groups by use of a mixed linear model that included the random variance of cat. Where there was a significant effect of treatment at $P \leq 0.05$, comparisons between treatments were made by use of least-squares means maintaining experiment-wise type-I error at 0.05. Thus, unless stated, where a difference is noted, $P \leq 0.05$.

Rectal temperature and hemodynamic and respiratory parameters were evaluated for differences across time and between treatments during the anesthetic period by use of a mixed linear model that included the random variance of cat and accounted for the repeated measurements over time. For those parameters that had a significant effect of treatment at $P \leq 0.05$, further exploration of the differences in fentanyl concentrations among treatments were evaluated by including these parameters in an ANCOVA analysis. Type-I error was maintained at $P \leq 0.05$ for the comparisons.[m]

Results

All data are reported as mean ± SEM. Before the induction of anesthesia, HR, RR, and rectal temperature were not significantly different between treatment groups (**Table 1**).

There were no significant differences between the SFC for each treatment group at time 0. Serum fentanyl concentrations for Iso-norm and Iso-hypo were 1.484 ± 0.4678 and 1.834 ± 0.6393 ng/mL, respectively. There was a significant reduction in SFC in the Iso-hypo group from 1 to 4 hours (**Fig 1**).

The mean SFC for cats in the Iso-norm group from

Table 1—Mean ± SEM values for rectal temperature, heart rate, respiratory rate, systolic blood pressure, and end-tidal carbon dioxide ($ETCO_2$) during and after 4 hours of isoflurane anesthesia with normothermia (Iso-norm) or hypothermia (Iso-hypo) in 7 cats

		Time from induction of anesthesia (h)																
Parameter	**Treatment**	**0†**	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**3.5**	**4**	**4.5**	**5**	**6**	**7**	**8**	**10**	**12**	**24**
Rectal temperature (°C)	Iso-norm	38.8 (0.4)	38.1*^{A} (0.3)	37.9*^{A} (0.2)	38.0*^{A} (0.2)	38.1*^{A} (0.2)	38.2*^{A} (0.2)	38.3^{A} (0.2)	38.3^{A} (0.2)	38.2* (0.2)	38.9^{A} (0.3)	39.3*^{A} (0.2)	39.3* (0.3)	39.6* (0.3)	39.4* (0.2)	39.0 (0.2)	39.1 (0.2)	39.1 (0.4)
	Iso-hypo	39.1 (0.2)	37.5*^{B} (0.3)	36.0*^{B} (0.4)	35.3*^{B} (0.3)	35.1*^{B} (0.2)	35.0*^{B} (0.1)	35.1*^{B} (0.1)	35.1*^{B} (0.1)	35.2*^{B} (0.0)	36.5*^{B} (0.3)	38.2*^{B} (0.2)	39.0 (0.2)	39.2* (0.2)	39.4* (0.1)	39.3* (0.2)	39.2* (0.2)	38.8 (0.1)
Heart rate (beats/min)	Iso-norm	194.8 (12.3)	138.0* (7.4)	129.7* (7.3)	131.0* (7.8)	131.8* (7.8)	133.7* (10.0)	139.6* (8.0)	153.7*^{A} (16.9)	142.3*^{A} (11.7)	189.0 (16.4)	168.0 (8.5)	182.5 (12.1)	184.0 (11.5)	185.7 (11.2)	169.1*^{A} (9.3)	186.0 (13.0)	174.8 (14.5)
	Iso-hypo	179.7 (11.1)	136.0* (5.3)	113.4* (2.2)	109.7* (3.8)	110.6* (4.6)	114.6* (6.1)	115.4* (6.0)	118.8*^{B} (6.0)	111.7*^{B} (2.8)	190.2 (13.1)	186.7 (6.0)	166.5 (14.5)	199.0 (12.0)	186.7 (9.8)	197.2^{B} (7.4)	190.0 (5.1)	199.3 (10.1)
Respiratory rate (breaths/min)	Iso-norm	42.3 (6.1)	12.5* (1.4)	11.6* (2.6)	11.2* (2.7)	10.6* (2.1)	9.8* (1.8)	10.7* (1.8)	14.0* (5.5)	15.4* (3.9)	28.0 (2.3)	35.4 (5.4)	35.4 (5.7)	36.4 (6.1)	33.7 (4.7)	37.1 (4.3)	40.8 (3.9)	38.3 (5.0)
	Iso-hypo	45.7 (6.2)	11.7* (1.5)	11.1* (1.8)	10.3* (1.9)	9.9* (1.80)	11.4* (2.1)	10.4* (1.9)	10.7* (1.8)	10.5* (1.9)	28.3* (1.3)	29.2* (2.2)	33.2* (3.5)	31.7* (2.7)	35.7 (3.4)	33.3* (2.7)	31.8* (3.4)	36.0 (2.0)
Systolic blood pressure (mm Hg)	Iso-norm	84.3 (3.4)	82.3 (7.4)	79.4 (6.5)	79.0 (8.8)	71.4 (8.0)	75.5 (10.70)	73.0 (7.15)	77.3 (11.6)	78.0 (13.3)	NA	NA	NA	NA	NA	NA	NA	NA
	Iso-hypo	81.3 (4.0)	85.0 (7.1)	88.6 (7.1)	82.8 (7.1)	76.1 (5.3)	73.8 (6.0)	65.4 (6.6)	65.4 (9.4)	58.3 (5.6)	NA	NA	NA	NA	NA	NA	NA	NA
$ETCO_2$ (mm Hg)	Iso-norm	41.0 (4.8)	43.7 (5.9)	48.4 (4.4)	46.7 (5.3)	52.6 (6.2)	54.7 (7.6)	57.3 (6.9)	57.0 (9.0)	60.7 (8.6)	NA	NA	NA	NA	NA	NA	NA	NA
	Iso-hypo	34.0 (2.9)	40.4 (3.2)	38.4 (3.7)	37.7 (5.8)	42.0 (7.6)	36.1 (3.9)	43.9 (9.4)	48.4 (9.4)	48.5 (7.9)	NA	NA	NA	NA	NA	NA	NA	NA

*Significantly different ($P < 0.05$) from value at time 0 for the same treatment group. †Values for heart rate and respiratory rate at time 0 recorded immediately before induction of anesthesia. Values for systolic blood pressure and $ETCO_2$ recorded immediately following induction of anesthesia.

^{A,B}For each parameter within a column, values with different superscript letters are significantly ($P \leq 0.05$) different.

NA = Not applicable.

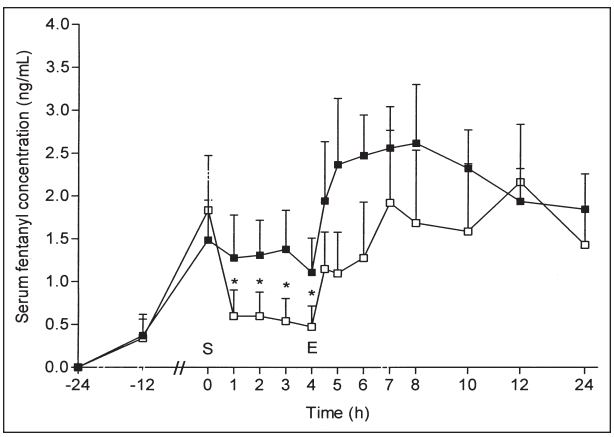

Figure 1—Mean ± SEM perianesthetic serum fentanyl concentrations associated with 4 hours of isoflurane anesthesia with normothermia (closed squares) or hypothermia (open squares) in 7 cats. *Significantly ($P < 0.05$) less than corresponding baseline (time 0) values. S = Start anesthesia. E = End anesthesia.

0 to 5 hours was 1.42 ng/mL, compared with 0.748 ng/mL for the Iso-hypo treatment group. However, partial $AUC_{0\text{-}5}$ for Iso-norm and Iso-hypo were 7.10 ± 2.395 and 3.74 ± 1.370 ng·h/mL, respectively, and the difference between the 2 treatment groups was not significant ($P = 0.14$).

Before the induction of anesthesia, rectal temperature was not significantly different between treatment groups. Compared with preinduction values, there was a significant reduction in temperature in the Iso-norm group from 0.5 to 2.5 hours and again at 4 hours. There was a significant increase in temperature in the Iso-norm group from 5 to 8 hours. Compared with preinduction values, there was a significant reduction in temperature in the Iso-hypo group from 0.5 to 5 hours. There was a significant increase in temperature in the Iso-hypo group from 7 to 12 hours. Temperature was significantly lower in the Iso-hypo group than that in the Iso-norm group from 0.5 to 5 hours. Mean ± SEM temperatures for Iso-norm and Iso-hypo for the 4-hour anesthetic period were 38.1°C ± 0.07 and 35.5°C ± 0.13, respectively.

Compared with preinduction values, there was a significant decrease in HR in both treatment groups from 0.5 to 4 hours. During the anesthetic period, HR for the Iso-norm treatment group was significantly greater than that for the Iso-hypo treatment group at 3.5 and 4 hours. Following anesthesia, HR for the Iso-hypo treatment group was significantly higher than that for the Iso-norm treatment group at 10 hours.

Before the induction of anesthesia, RR was not significantly different between groups. Compared with preinduction values, there was a significant reduction in RR for both treatment groups from 0.5 to 4 hours. This reduction persisted in the Iso-hypo treatment group from 4.5 to 7 hours and was significant again at 10 and 12 hours. There were no significant differences between the treatment groups for SBP or $ETCO_2$ during the anesthetic period.

One cat died during the Iso-hypo treatment. This cat had been exposed previously to the Iso-norm treat-

ment with no apparent adverse effects. On the day of the Iso-hypo trial, the SFC for this cat was 4.98 ng/mL at the time of induction of anesthesia. The hourly SFCs for 1, 2, and 3 hours were 0.68, 0.93, and 0.70 ng/mL, respectively. Heart rate, SBP, and Spo_2 were within reference limits during the anesthetic period before death. The RR before induction was 28 breaths/min. Following the induction of anesthesia, the RR was 10 breaths/min. The RR declined during the next 3 hours to a level of 2 breaths/min. This gradual decline in RR was accompanied by a gradual increase in $ETco_2$. Immediately following the induction of anesthesia, the $ETco_2$ was 41 mm Hg. The $ETco_2$ gradually increased over the next 3 hours to 98 mm Hg. At this point, the cat went into complete respiratory and cardiovascular arrest and was not successfully resuscitated. The SFC at the time of arrest was < 0.25 ng/mL (below the limit of detection of the assay). Rectal temperature at the time of arrest was 35.1°C. Necropsy findings were unremarkable.

Discussion

Results of this study indicated an association between hypothermia during isoflurane anesthesia and a reduction in SFC obtained with transdermal administration. Detected serum concentrations of fentanyl during transdermal administration are the result of several factors, including the release of fentanyl from the transdermal system, diffusion of fentanyl through the epidermis, movement into the vascular dermis, diffusion into the vascular system, movement of fentanyl from the vascular space into compartments outside the central compartment, and elimination of fentanyl by excretion or metabolism.[13] Hypothermia reduces cutaneous blood flow, and vasoconstriction associated with extreme cold stress can virtually abolish skin blood flow.[14-19] The vascular response to cold stress is influenced by many factors, including the location of the site in which the vascular response is measured, magnitude and duration of hypothermia, and body type and weight.[16-18] In this study, reduction in cutaneous blood flow may have reduced the fentanyl uptake from dermal depots and caused the observed decrease in SFC in the central compartment. Although there was a significant reduction in temperature in the Iso-norm treatment group during most of the anesthetic period, it does not appear to have been of a magnitude sufficient to induce changes in the SFC.

Changes in cardiovascular function not detected by measuring HR and SBP may have been responsible for the changes in SFC. Because the major site of elimination of fentanyl is the liver and its clearance approximates hepatic blood flow,[20] changes in cardiac output that cause significant alterations in hepatic blood flow could alter SFC. However, HR and SBP were used as indicators of cardiovascular performance in this study. Although the relationship of HR and SBP with cardiac output and hepatic blood flow is direct, it is not always linear. Because there were no significant changes in the measured cardiovascular parameters that were coincident with the pattern of change in SFC and the pattern of changes in SFC would suggest increased rather than decreased hepatic clearance, any changes in cardiac output or hepatic blood flow that were responsible for an increase in the clearance of fentanyl would have occurred without any concomitant changes in HR or SBP.

Because hypothermia reduces cutaneous blood flow, it would seem more reasonable to speculate that the changes in SFC were induced by changes in delivery rather than clearance. Thus, the transfer of fentanyl from the dermal space to the vascular compartment is reduced. Despite significant reductions in SFC during hypothermia and anesthesia, the partial AUCs for the anesthetic period and first postanesthetic hour were not significantly different between treatment groups. The mean SFC for each treatment group during that time period was within the range of concentrations purported to be associated with analgesia,[3,21] although certain investigators have not been able to determine a significant correlation between SFC and pain score.[1] Thus, the observed changes in SFC that were a result of anesthesia and hypothermia may not be associated with an important change in clinical effect.

Transdermal administration of fentanyl in the perianesthetic period has the potential to induce clinically important respiratory depression as well as delayed recovery because of prolonged sedation.[22,23] Humans are extremely sensitive to the effect of opioids on respiratory function, and the use of the poorly titratable transdermal administration of fentanyl is contraindicated in the perioperative period.[24-26] Although clinically relevant doses of opioids administered to dogs and cats may not cause significant respiratory depression,[27] the administration of higher doses may cause hypercapnia and hypoxemia as a consequence of hypoventilation.[28] Because transdermal administration of fentanyl is not highly titratable and there is variability in the SFC with transdermal administration,[4] the potential exists for the development of substantial respiratory depression in the perianesthetic period, particularly when a synergistic effect with other respiratory depressants may be precipitated. However, in the postoperative period following cranial abdominal exploratory laparotomy and diaphragmatic herniorrhaphy, transdermal administration of fentanyl to dogs is not associated with arterial blood gas values that are substantially different from those obtained from dogs receiving buprenorphine administered IV. Arterial $Paco_2$ during the postoperative period did not exceed 45 mm Hg in response to either treatment.[29]

In this study, arterial blood gas analyses were not performed. However, $ETco_2$ was monitored throughout the anesthetic period. Although there were no significant differences in $ETco_2$ between the 2 treatment groups, $ETco_2$ for the normothermic treatment group was more consistently outside the upper reference limit than was the $ETco_2$ for the hypothermic treatment group. This observation suggests that normothermic cats anesthetized with isoflurane and receiving fentanyl transdermally may be at risk for the development of clinically important respiratory depression. The single death that occurred during this study did so during isoflurane anesthesia with hypothermia. Although the reason for this death remains unknown, the high SFC at the beginning of the anesthetic period

plus the high ET_{CO_2} and low respiratory rate at the time of arrest suggests that respiratory depression may have played a role. Although this death was a single occurrence, it does suggest that malignant hypoventilation requiring support can occur in a patient receiving fentanyl transdermally during anesthesia with a modest concentration of isoflurane and moderate hypothermia.

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[d]Duragesic, Janssen Pharmaceutical Products LP, Titusville, NJ.

[e]Elastikon, Johnson & Johnson, Arlington, Tex.

[f]Vetrap, 3M Corp, St Paul, Minn.

[g]Normosol-R, Abbott Laboratories, North Chicago, Ill.

[h]Model 811-B, Parks Medical Electronics Inc, Aloha, Ore.

[i]Passport XG Multifunction Monitor, Datascope Corp, Paramus, NJ.

[j]BIOCHEM 9100 Multigas Monitor, BCI Inc, Waukesha, Wis.

[k]Veno-Cath-16, Venisystems, Abbott Ireland, Sligo, Republic of Ireland.

[l]Coat-A-Count Fentanyl, Diagnostics Products Corp, Los Angeles, Calif.

[m]SAS, version 8.0, SAS Institute Inc, Cary, NC.

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