LABORATORY INVESTIGATIONS

Anesthesiology
83:535–542, 1995

Lippincott–Raven Publishers

Effect of Fentanyl on the Minimum Alveolar Concentration of Isoflurane in Swine

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Background: **Fentanyl is used in anesthetic protocols for swine, but there are no reports on its potency in this species. This study measured the extent to which fentanyl reduces the minimum alveolar concentration of isoflurane (MAC_{ISO}) in swine.**

Methods: **Sixteen swine were randomly assigned to four groups. For each group, baseline MAC_{ISO} was determined, and three groups received two of three fentanyl infusions as follows: 50 $\mu g \cdot kg^{-1} \cdot h^{-1}$ intravenously followed by 100 $\mu g \cdot kg^{-1} \cdot h^{-1}$, 50 $\mu g \cdot kg^{-1} \cdot h^{-1}$ followed by 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$, or 100 $\mu g \cdot kg^{-1} \cdot h^{-1}$ followed by 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (n = 8 for each dosage). A loading dose of fentanyl preceded each infusion. Each infusion was maintained for 60 min before initiating minimum alveolar concentration determination. The infusions were maintained throughout the period of minimum alveolar concentration determination. Plasma fentanyl samples were obtained after 30 min of each infusion, and plasma fentanyl and hemodynamic parameters were obtained immediately before stimulating swine for the final isoflurane concentration used in determining minimum alveolar concentration. A fourth group, control animals, received saline infusions. After each infusion, the MAC_{ISO} was redetermined. Minimum alveolar concentration was determined using incremental changes in isoflurane concentrations until gross purposeful movement resulted when using a hemostat stimulus applied for 1 min to a rear dewclaw.**

Results: **MAC_{ISO} for controls was 2.19 ± 0.17% (mean ± SEM) and changed minimally over time (−0.13 ± 4.77%). MAC_{ISO} decreased significantly ($P \leq 0.01$) 24.5 ± 3.2%, 29.9 ± 4.8%, and 45.9 ± 5.5% with fentanyl dosages of 50, 100, and 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$, respectively. Corresponding plasma fentanyl concentrations were 14 ± 1 ng/ml, 26 ± 3 ng/ml, and 59 ± 5 ng/ml, respectively. A ceiling effect on reduction of MAC_{ISO} was not observed. Changes over time or between groups were not observed for arterial blood gas tensions, blood pressure, heart and respiratory rate, or body temperature.**

Conclusions: **These fentanyl dosages are larger than those commonly used in humans and other species. Anesthetic protocols using fentanyl for swine should be designed with the knowledge that a fentanyl infusion of 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$ contributes approximately a 50% MAC_{ISO} equivalent. (Key words: Analgesics, opioid: fentanyl. Anesthetics, volatile: isoflurane. Animal: swine. Potency: minimum alveolar concentration.)**

This article is accompanied by an editorial. Please see: Steffey EP: Isoflurane-sparing effect of fentanyl in swine: Relevance and importance. ANESTHESIOLOGY 83:446–448, 1995.

SWINE have been adopted as a common model for cardiovascular[1–10] and transplantation[11–14] research because of the physiologic and anatomic similarities of swine to humans. In these studies, fentanyl was administered intravenously in dosages ranging from 4 to 50 $\mu g \cdot kg^{-1} \cdot h^{-1}$ as part of the anesthetic protocol.[12] These dosages, however, appear to be extrapolated from dosages used in humans and are not based on pharmacologic data for swine. These dosages are "derived from other laboratories" [1] or from "methods for cardiac surgery in man [because] the veterinary anesthesia literature is based primarily on agricultural procedures and is not relevant [to cardiovascular research]." [1] However, it is reasonable to question whether a particular anesthetic protocol used in one species should be transferred directly to another, especially in view of the fact that the resulting data can be significantly influenced by neurohumoral responses to pain.

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Received from the Department of Clinical Sciences and Diagnostic Laboratory, College of Veterinary Medicine, Cornell University, Ithaca, New York. Submitted for publication October 24, 1994. Accepted for publication April 5, 1995. Supported in part by a grant from the Cornell Alumni Unrestricted Funds and a grant from the President's Council for Cornell Women. Coat-a-Count fentanyl assay kits were donated by Diagnostics Products Corporation. Presented at the Fifth International Veterinary Anesthesia Conference, Guelph, Canada, August 1994.

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Studies have shown that there are interspecies differences in pharmacokinetic and pharmacodynamic properties of opioid agonists.[15–20] A single bolus of fentanyl, at dosages of 30–50 μg/kg for infants and 20–100 μg/kg for adults, has been administered as the sole anesthetic for humans with cardiovascular disease.[17] However, the anesthetic efficacy of a single bolus of fentanyl, as large as 3,000 μg/kg, to dogs has been debated.[16] More specifically, swine require larger concentrations of morphine than either dogs or primates,[15] and primates respond to fentanyl in a manner similar to humans.[18] Because both morphine and fentanyl are opioid agonists, fentanyl dosages acceptable for humans may be inadequate for swine used in research protocols.

To date, there are no reports on the efficacy of fentanyl as an anesthetic in swine. Numerous investigations have measured the anesthetic potency of opioid agonists in various species by performing minimum alveolar concentration reduction studies.[21,22] The goal of this study was to measure the extent to which fentanyl reduced the minimum alveolar concentration of isoflurane (MAC_{ISO}) in swine.

Methods and Materials

This study was approved by the Cornell University Animal Care and Use Committee. Unpremedicated, 4–5-month-old, female Yorkshire-cross swine (n = 16), weighing 27 ± 2.2 kg (mean ± SD), were anesthetized *via* mask with 4–5% isoflurane (Aerrane, Anaquest, Madison, WI) in 100% O_2 delivered at 5 l/min. Each pig was orotracheally intubated, and the concentration of isoflurane was reduced to 2–3% in oxygen delivered at 2 l/min. Animals were placed in lateral recumbency. Atropine (0.04 mg/kg, intramuscular) was administered to decrease secretions and protect against fentanyl-induced bradycardia. The lungs were mechanically ventilated to maintain normocapnia (Pa_{CO_2} 35–45 mmHg). Two catheters were inserted percutaneously into auricular veins, one for administering fluids and the other for infusing fentanyl or saline. A catheter was inserted percutaneously into a femoral artery for continuous monitoring of systemic arterial blood pressures and for obtaining arterial blood samples. A lead II electrocardiogram was used to monitor heart rate and rhythm, and an agent-specific, photoacoustic gas monitor (Type 1304, Brüel and Kjaer, Naerum, Denmark) measured inspired and expired gases, including end-tidal isoflurane and carbon dioxide. Lactated Ringer's solution was infused intravenously throughout the study to maintain a systemic mean arterial blood pressure greater than 60 mmHg. A rectal temperature probe monitored body temperature, which was maintained at 38–39°C by using a warm water-circulating heating pad to warm the swine or a fan and isopropyl alcohol to cool the swine.

Using a random number table, 16 swine were divided equally into four groups. Three of these groups were randomly assigned to one of three different protocols. Each protocol consisted of two fentanyl infusions as follows: 50 $\mu g \cdot kg^{-1} \cdot h^{-1}$ followed by 100 $\mu g \cdot kg^{-1} \cdot h^{-1}$, 50 $\mu g \cdot kg^{-1} \cdot h^{-1}$ followed by 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$, or 100 $\mu g \cdot kg^{-1} \cdot h^{-1}$ followed by 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Thus, eight swine received each dosage. Before each infusion, a loading dose of fentanyl was administered, as described below. The fourth group, the control group, received infusions of normal saline to evaluate the effect of time on MAC_{ISO}.

For each group, baseline MAC_{ISO} was determined before the pigs received fentanyl. The first infusion was administered for 60 min, after which MAC_{ISO} was redetermined. After MAC_{ISO} was redetermined, the second 60-min infusion was administered, and MAC_{ISO} was determined again.

Fentanyl was administered as fentanyl citrate (Sigma, St. Louis, MO) dissolved in 0.9% normal saline. A loading dose for each maintenance infusion rate was determined using standard pharmacokinetic equations, where loading dose = $V_D \cdot C_P$ and maintenance infusion rate = $CL \cdot C_P$; V_D = volume of distribution, C_P = plasma fentanyl concentration, and CL = clearance of fentanyl. V_D and CL were set at 216 ml/kg and 2.42 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively, based on previously reported pharmacokinetic data of fentanyl in swine.[20] The initial loading dose was calculated for the appropriate maintenance infusion rate using these data, whereas the second loading dose and maintenance infusion rate were corrected for the theoretical plasma fentanyl concentration already present because of the first fentanyl infusion (see table 1 for specific loading doses for each group). To blind the investigators to the type (saline *vs.* fentanyl) and dosage of solution being infused, loading doses for the first and second infusions were standardized to 60-ml volumes, and both infusion volumes were standardized for administering the test solution at 100 ml/h. For each infusion, plasma fentanyl samples were obtained after 30 min and when MAC_{ISO} was determined to ascertain whether blood fentanyl concentrations were at steady-state.

At the beginning and end of the study, blood was obtained for measuring hematocrit and total solids. During baseline MAC_{ISO}, each pig received only lactated Ringer's solution. During the first and second infusions, the test solution and lactated Ringer's were administered concurrently, the latter for maintaining blood pressure.

The method used for determining MAC_{ISO} has been described previously.[23,24] Briefly, an end-tidal isoflurane concentration was maintained for a minimum of 15 min such that the difference between the inspired and expired concentration of isoflurane was no more than 0.1%. This was done to ensure steady-state equilibration of alveolar isoflurane with that in arterial blood (brain). At the end of each 15-min equilibration period, end-tidal gases, heart and respiratory rates, blood pressures, fluid requirements, and temperatures were recorded. Each pig was stimulated with a hemostat clamped to full ratchet lock on a rear dewclaw, and the limb was moved cranially and caudally for a minute using the hemostat. If there was no purposeful response to stimulation, the end-tidal isoflurane concentration was reduced 10–20%, 15 min was allowed for equilibration, and the stimulus was repeated. Additional decrements of the end-tidal isoflurane concentration were made until there was purposeful movement. The isoflurane concentration was increased 10%, and after the equilibration period, the stimulus was repeated. The isoflurane concentration halfway between that allowing and that preventing movement, to the nearest 0.05%, was the MAC_{ISO} for that pig. Once MAC_{ISO} was determined, end-tidal carbon dioxide was recorded, and an arterial blood sample was simultaneously collected for analysis of plasma fentanyl, *p*H, and blood gas tensions. All animals were allowed to recover from anesthesia.

Blood gas samples were stored on ice and analyzed within 30 minutes of sampling on an automated blood gas analyzer (ABL2, Radiometer, Copenhagen, Denmark). Results were corrected for body temperature. Hematocrits were determined by centrifugation of blood in a microhematocrit centrifuge, and total solids were determined with a refractometer. Total solids is clinically thought to be equivalent to total protein, but a refractometer does not distinguish between total protein and small amounts of other particles, which may alter the reflectance of a solution. Plasma samples and solution samples from the first and second infusions were stored at −30° until assayed for fentanyl concentration using a solid-phase radioimmunoassay kit (Coat-A-Count fentanyl, Diagnostic Product, Los Angeles, CA). These assays measure fentanyl base, which is 64% of the weighed fentanyl citrate used in the infusions. All samples were compared with results obtained from a second commercial radioimmunoassay kit (Research Diagnostics, Flanders, NJ). In addition, samples from the stock fentanyl solution, from commercially available medical fentanyl citrate (fentanyl citrate injection, Abbott, Abbott Park, IL), from both assay kit standards, and from randomly selected experimental plasma samples were assayed for fentanyl by infusion atmospheric pressure ionization mass spectrometry. This was done to verify that the stock chemical compound had equal fentanyl activity as the commercially available compound, and that both kits were accurate in measuring fentanyl.

Table 1. Loading Doses of Fentanyl Each Animal Received before Each Infusion for the Three Experimental Groups

Group	Loading Dose ($\mu g/kg$)	
	First Infusion	Second Infusion
1	74.4	74.4
2	74.4	223
3	148.8	148.8

Loading doses were calculated from the pharmacokinetic data in reference 20 for the first infusion as well as the theoretical plasma fentanyl present for the second infusion. Group 1 received 50 $\mu g \cdot kg^{-11} \cdot h^{-1}$ followed by 100 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Group 2 received 50 $\mu g \cdot kg^{-1} \cdot h^{-1}$ followed by 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Group 3 received 100 $\mu g \cdot kg^{-1} \cdot h^{-1}$ followed by 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$. n = 4 for each group.

This study was designed as an incomplete block design. The mean percent reductions in MAC_{ISO} and the absolute changes in MAC_{ISO} from baseline associated with each fentanyl dosage (50, 100, and 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$) were compared using analysis of variance for incomplete block designs.[25] The analysis was carried out using the general linear models procedure in SAS.[26] Statistical significance was conservatively set at $P \leq 0.01$ to adjust for multiple comparisons.[27] Because there was some concern that the order of treatments might influence the results, mean percent reduction in MAC_{ISO} was compared within treatment groups, where data existed, using Student's *t* test.[28] The association between the MAC_{ISO} and plasma fentanyl concentration in each pig was assessed with Pearson's correlation coefficient and simple linear regression.[28]

Measurements of potentially confounding factors (temperature, *p*H, Pa_{O_2}, or Pa_{CO_2}) were compared

across the treatment groups (*i.e.,* fentanyl dosages) using analysis of variance. Tukey's method for multiple comparisons was used to evaluate pairwise comparisons.[25] Comparisons of continuous variables between two groups were compared with the Student's *t* test (when the groups were independent) and with the paired *t* test (when the data were dependent).

Results

Results are expressed as mean ± SEM. Variables known to affect minimum alveolar concentration (temperature, *p*H, Pa_{O_2}, or Pa_{CO_2}) were unchanged and within normal limits throughout the study (table 2). Each animal received 15 ± 1 $ml \cdot kg^{-1} \cdot h^{-1}$ of fluids during the 5.3 ± 0.3-h study. Although not statistically significant, blood pressure tended to increase as fentanyl dosages increased among the groups (table 2). Within treatment type, there was no significant difference in the percent reduction in MAC_{ISO} among pigs receiving 100 $\mu g \cdot kg^{-1} \cdot h^{-1}$ fentanyl as the first treatment and those receiving this dose preceded by 50 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Similarly, there was no difference between pigs receiving 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$ preceded by 50 $\mu g \cdot kg^{-1} \cdot h^{-1}$ compared to those receiving this dose preceded by 100 $\mu g \cdot kg^{-1} \cdot h^{-1}$. All groups had obtained a steady-state level of plasma fentanyl as evidenced by comparing middle- and end-of-infusion plasma fentanyl concentrations (table 3).

Previous research has indicated that minimum alveolar concentration does not vary over time.[23] Data from the control group (no fentanyl) confirmed this, and these data were not included in further comparisons in the effectiveness of different fentanyl infusion dosages. There was, however, wide variation in the value of MAC_{ISO} among these four animals (fig. 1), and one of these had an unexplained 28% decrease in MAC_{ISO} during the second infusion. Despite this individual variation, MAC_{ISO} did not change statistically throughout the study for these four animals.

Mean plasma fentanyl concentrations and all MAC_{ISO} data are provided in table 3. The baseline MAC_{ISO} was not different between groups or compared to controls. There was a dose-related decrease in MAC_{ISO} as the dose of fentanyl increased (fig. 2). The MAC_{ISO} at each dosage of fentanyl was statistically different from the other two dosages. Among individual animals, the percent reduction in MAC_{ISO} for swine receiving 50 $\mu g \cdot kg^{-1} \cdot h^{-1}$ ranged from 10% to 37%; for those receiving 100 $\mu g \cdot kg^{-1} \cdot h^{-1}$, the reduction in MAC_{ISO} ranged from 11% to 48%; and for 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$, it ranged from 25% to 63%.

There was a statistically significant ($P \leq 0.01$) negative correlation when MAC_{ISO} ($r = -0.59$; fig. 3) was plotted against the plasma fentanyl level for each animal. One animal with a blood fentanyl concentration of 89 ng/ml had a relatively large MAC_{ISO} and might be considered to be an outlier. This animal received 100 $\mu g \cdot kg^{-1} \cdot h^{-1}$ fentanyl followed by 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and had high MAC_{ISO} values for baseline and both infusions (2.68%, 2.20%, and 2.00%, respectively). When all three MAC_{ISO} determinations from this pig are removed, the MAC_{ISO} *versus* plasma fentanyl becomes even more highly correlated ($r = -0.74$).

Discussion

Fentanyl is often used in anesthetic protocols for research animals, particularly swine. Prior studies using fentanyl in swine, however, did not focus on its anes-

Table 2. Blood Gas and Hemodynamic Data from Swine Receiving Several Infusions of Fentanyl

Dosage* ($\mu g \cdot kg^{-1} \cdot h^{-1}$)	pH_a	Pa_{CO_2} (mmHg)	Pa_{O_2} (mmHg)	ABE (mEq/L)	HCT (%)	TS (g/dl)	ET_{CO_2} (mmHg)	HR (beats/min)	MAP (mmHg)	Temperature (°C)
0	7.422 ± 0.005	42 ± 1	407 ± 19	2.2 ± 0.4	30 ± 1	5.7 ± 0.1	39 ± 1	113 ± 3	56 ± 2	38.7 ± 0.0
50	7.354 ± 0.017	45 ± 2	376 ± 22	−0.7 ± 0.4	ND	ND	43 ± 2	133 ± 5	60 ± 1	39.0 ± 1
100	7.373 ± 0.021	45 ± 2	380 ± 23	0.2 ± 0.7	30 ± 2	5.3 ± 0.2	42 ± 1.3	135 ± 6	62 ± 3	38.8 ± 0.0
200	7.402 ± 0.015	42 ± 2	413 ± 28	0.7 ± 0.4	28 ± 1	5.0 ± 0.2	39 ± 1	131 ± 8	68 ± 4	38.9 ± 0.1

Values are mean ± SEM.

ABE = arterial base excess; ET_{CO_2} = end-tidal CO_2; HCT = hematocrit; HR = heart rate; MAP = mean arterial pressure; ND = no data; Pa_{CO_2} = arterial partial pressure of carbon dioxide; Pa_{O_2} = arterial partial pressure of oxygen; pH_a = arterial *p*H; TS = total solids.

* Baseline data are for n = 12, fentanyl dosages are for n = 8.

Table 3. Plasma Fentanyl Conc
from Baseline MAC_{ISO} after Fen

Fentanyl Infusion ($\mu g \cdot kg^{-1} \cdot h^{-1}$)	30-min Fentany
50	14 ± 1
100	26 ± 3
200	55 ± 3

Values are mean ± SEM; n = 8 swine
MAC_{ISO} = minimum alveolar concentra
* Mean values are significantly differe
$\mu g \cdot kg^{-1} \cdot h^{-1}$ *versus* 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$

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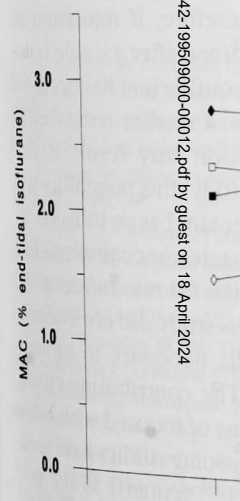

Fig. 1. The MAC_{ISO} for contro
after two 60-min infusions

Table 3. Plasma Fentanyl Concentrations, Baseline MAC_{ISO}, MAC_{ISO} after 60-minute Fentanyl Infusion, and Percent Reduction from Baseline MAC_{ISO} after Fentanyl Infusion in Swine

Fentanyl Infusion ($\mu g \cdot kg^{-1} \cdot h^{-1}$)	30-min Plasma Fentanyl (ng/ml)	Final Plasma Fentanyl (ng/ml)	Baseline MAC_{ISO} (%)	MAC_{ISO} (%) after Infusion	% Reduction from Baseline in MAC_{ISO}
50	14 ± 1	14 ± 1	2.51 ± 0.08	1.89 ± 0.09	25 ± 3*
100	26 ± 3	26 ± 3	2.40 ± 0.13	1.65 ± 0.09	30 ± 5*
200	55 ± 3	59 ± 5	2.50 ± 0.12	1.35 ± 0.11	46 ± 6*

Values are mean ± SEM; n = 8 swine per infusion.

MAC_{ISO} = minimum alveolar concentration of isoflurane.

* Mean values are significantly different: 50 $\mu g \cdot kg^{-1} \cdot h^{-1}$ *versus* 100 $\mu g \cdot kg^{-1} \cdot h^{-1}$ ($P = 0.002$); 50 $\mu g; \cdot kg^{-1} \cdot h^{-1}$ *versus* 200 $\mu g\text{-}kg^{-1} \cdot h^{-1}$ ($P = 0.0001$); 100 $\mu g \cdot kg^{-1} \cdot h^{-1}$ *versus* 200 $\mu g \cdot kg^{-1} h^{-1}$ ($P = 0.004$).

thetic efficacy.[1,3–14] Information from these studies is not useful because anesthetic dosages were not provided[9,13] or neuromuscular blockers were used.[1–9,11–14] Neuromuscular blockade makes depth of anesthesia difficult to determine, especially when hemodynamic variables and other monitored signs are experimentally manipulated, and are therefore unreliable. The goal of this study was to measure the extent to which fentanyl reduced the MAC_{ISO} in swine, thus providing information on its potency in this species. The lowest fentanyl infusion used in this study was based on the largest fentanyl infusion reported for swine.[1]

In this study, the mean control value for MAC_{ISO}, 2.19%, was similar to previous reports of 2.04%[29] and 2.2%[24] for swine. There was a decrease in MAC_{ISO} with increasing concentrations of plasma fentanyl. The lowest infusion rate, 50 $\mu g \cdot kg^{-1} \cdot h^{-1}$, produced a 24% decrease in MAC_{ISO}, whereas the largest infusion rate, 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$, produced only a 45% reduction in MAC_{ISO}. In a similar study in humans, investigators reported that plasma fentanyl concentrations as little as 3 ng/ml resulted in a 63% decrease in MAC_{ISO}.[22] In this pig study, plasma fentanyl concentrations of 59 ng/ml, 20 times greater than in humans, resulted in only a 45% decrease in MAC_{ISO}. In dogs, plasma fentanyl concentrations of 30 ng/ml resulted in a 65% reduction in the minimum alveolar concentration of enflurane,[21]

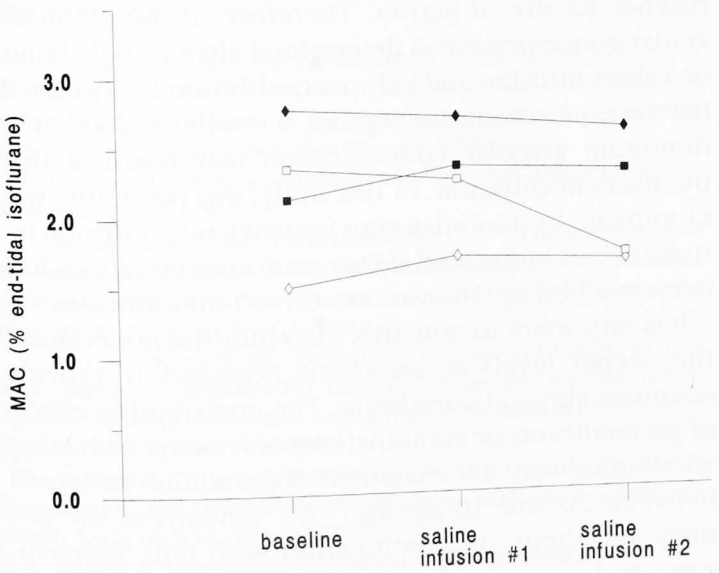

Fig. 1. The MAC_{ISO} for control pigs (n = 4) during baseline and after two 60-min infusions of saline.

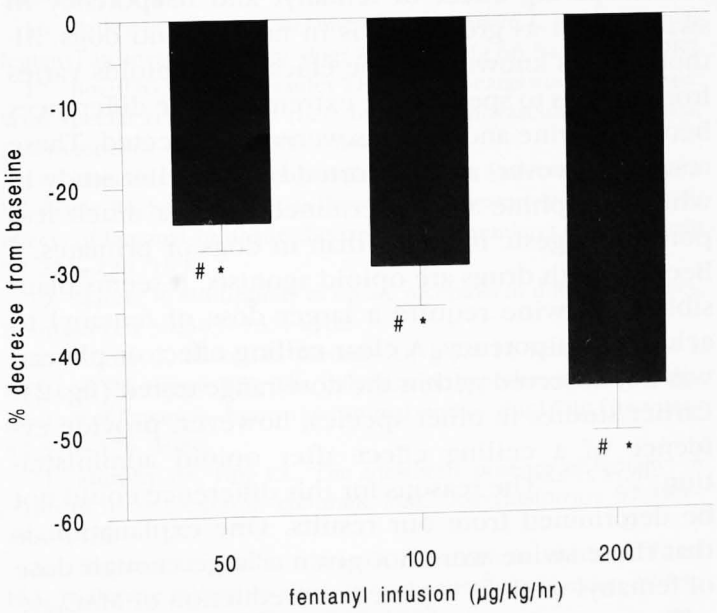

Fig. 2. The percent difference between baseline MAC_{ISO} and MAC_{ISO} after 60-min fentanyl infusions in swine (mean ± SEM, n = 8 for each group). All infusions resulted in a significant decrease in MAC_{ISO}* from baseline and significant differences were found among all infusions# ($P \leq 0.01$).

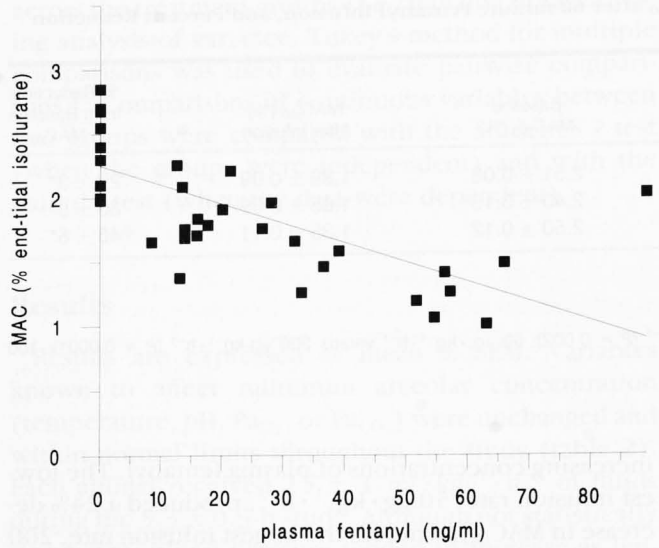

Fig. 3. Individual MAC_{ISO} values obtained at individual plasma fentanyl concentrations for all pigs receiving fentanyl. Zero plasma fentanyl concentrations correspond to the baseline MAC_{ISO} determinations for these pigs. Regression equation was $y = 2.0 - 0.01x$, $r^2 = -0.59$, and was statistically significant ($P \leq 0.01$).

but in the current study, 26 ng/ml plasma fentanyl concentration resulted in only a 30% reduction in MAC_{ISO}. It appears that the minimum alveolar concentration-sparing effect of fentanyl and its potency in swine is not as great as it is in humans and dogs. Although it is known that the efficacy of opioids varies from species to species, the extremely large differences between swine and humans were not expected. These results, however, are supported by an earlier study in which morphine was determined to be a much less potent analgesic in swine than in dogs or primates.[15] Because both drugs are opioid agonists, it seems plausible that swine require a larger dose of fentanyl to achieve equipotency. A clear ceiling effect or plateau was not observed within the dose range tested (fig. 2). Earlier studies in other species, however, provide evidence of a ceiling effect after opioid administration.[16,18,21,22] The reasons for this difference could not be determined from our results. One explanation is that these swine were not given a large enough dose of fentanyl to show a plateau in reduction of MAC_{ISO}.

The reason for the smaller reduction of MAC_{ISO} compared to other studies is unclear. Differences in acid-base status, temperature, carbon dioxide, electrolytes, and hemodynamics can affect minimum alveolar concentration, but these variables remained within normal range during our study and in the other comparative studies. Minimum alveolar concentration also may vary depending on differences in application of the supramaximal stimulus (*e.g.*, duration, moving the leg or not), evaluation of responses to the stimuli, or the type of inhalant anesthetic being tested. However, it seems unlikely that minor differences in these factors would account for the large differences observed between species. Species differences in opioid receptor type, number or distribution may account for some of the differences observed.[19,30] Although minimal data are available, fentanyl and morphine appear to have different pharmacokinetics in swine than in dogs and, potentially, other species.[15,20,31]

Another potential cause for differences in the reduction of MAC_{ISO} compared to other studies is that our swine may have developed acute tolerance to the fentanyl. Tolerance after a continuous infusion or multiple intermittent boluses has been reported as a potential reason for differences in studies evaluating the anesthetic and analgesic effects of fentanyl in dogs.[16,32] Evidence of acute tolerance was not apparent in this study, however, because the same decrease in MAC_{ISO} was found for comparable plasma fentanyl concentrations, regardless whether that level was attained during the first or second infusion.

One further explanation for study differences may be the apparent hysteresis that has been reported to occur between plasma fentanyl concentration and its physiologic effects.[22] That is, there is a lag before fentanyl reaches its site of action. Therefore, if minimum alveolar concentration is determined after a single bolus or a short infusion and before equilibrium has occurred between plasma and receptors, a smaller reduction in minimum alveolar concentration may result at that plasma concentration. In this study, this possibility was eliminated by administering fentanyl as an infusion instead of as a bolus, and steady-state concentrations had been reached by 30 min into the 60-min infusion.

It is important to note that this study did not evaluate the deeper levels of anesthesia necessary to provide adequate surgical anesthesia. The contributing effects of premedicants or combinations of fentanyl with other anesthetics were not examined. Some studies have used between 20 and 50 $\mu g \cdot kg^{-1} \cdot h^{-1}$ fentanyl as the primary anesthetic, in combination with only premedicants and paralysis.[1,3] Our data show, however, that a fentanyl infusion of 50 $\mu g \cdot kg^{-1} \cdot h^{-1}$ is not adequate as

a sole anesthetic in swine because it reduces MAC_{ISO} by only 25%. Furthermore, fentanyl at 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$ reduces MAC_{ISO} an average of 45%. Therefore, none of the dosages tested in this study should be expected to produce acceptable, complete anesthesia in swine. Adequate anesthesia may be obtained when fentanyl is combined with other anesthetics, but other drugs must be used according to pharmacologic data for swine and not based on human dosages.

In conclusion, results from the current study indicate that fentanyl infusions of 50–200 $\mu g \cdot kg^{-1} \cdot h^{-1}$ reduce the minimum alveolar concentration of isoflurane in swine but not to the same degree as has been found in other species. Therefore, fentanyl dosages currently used in research involving swine should be evaluated carefully by the investigator to ensure minimal distress to the animal and to prevent collecting misleading data. Protocols should be designed with the knowledge that dosages up to 200 $\mu g \cdot kg^{-1} \cdot h^{-1}$ contribute approximately a 50% MAC equivalent. Extreme care should be taken when applying anesthetic protocols developed for humans to other species, such as swine.

The authors acknowledge the patience and persistence of the Diagnostic Laboratory and Dr. Thomas Reimers, for the blood fentanyl results, and Dr. Tim Wachs, for mass spectrometric fentanyl concentration assays. The authors also thank Jeanne Brohart, for technical expertise; Denise Hine, for secretarial assistance; and Jerry Decker, VMTH chief pharmacist, for drug preparation throughout this project.

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Anesthesiology
83:543–551, 1995

Opioid Agoni Neurotransm

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Background: Stimulation of can modulate cholinergic neu duce bronchoconstriction. T against bronchoconstriction halation of opioids as a meth in an opioid concentration a protect against bronchocons be insufficient when opioids a techniques. In addition, new oped that could more selecti bronchoconstriction.

Methods: The effect of three contractile response to elec studied in isolated muscle st vine trachea (upper, oblaryng lower, or carinal).

Results: The selective κ agon N-(2-1-pyrrolidinyl) cyclohe H) and the selective μ-opioid enkephalin (DAMGO) reduce < 0.001, respectively) the co tenuation of the contractile centration-dependent ($P < 0$ low stimulating frequencies the contractile response by D ($P < 0.01$). The selective δ-o penicillamine[5]-enkephalin h contractile response to EFS (icant differences among the their responses to the select = 0.50) and DAMGO (P = 0.44 altered the contractile respo > 0.21, respectively), suggest a prejunctional effect. The a

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Received from the Servizio d
Nazionale per la Ricerca sul Ca
publication January 23, 1995.
1995. Presented in part at the sec
Society of Anesthesiologists, Bru
Company, Kalamazoo, Michigan

Address reprint requests to D
Ricerca sul Cancro, Viale Bened