COMPARISON OF HAEMODYNAMIC EFFECTS OF ANAESTHETIC DOSES OF ALPHAPRODINE AND SULFENTANIL IN THE DOG

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ABSTRACT

The haemodynamic effects of equi-anaesthetic doses of alphaprodine and sulfentanil were evaluated in mongrel dogs ventilated mechanically. The effects of the addition of atropine were assessed for each drug, as were the effects of breathing nitrous oxide 60 per cent with oxygen and nitrogen 60 per cent with oxygen and the administration of naloxone.

The results of this study demonstrate that anaesthetic doses of sulfentanil produce little change in cardiovascular dynamics in atropinized dogs and only small changes in dogs without atropine premedication, irrespective of the infusion rate. In contrast alphaprodine causes a significant cardiovascular depression irrespective of the presence or absence of atropine premedication. Naloxone reversed the anaesthetic effects in all dogs anaesthetized with alphaprodine but did not reverse the anaesthetic state in any dog given sulfentanil.

Our data suggest that sulfentanil deserves evaluation as a narcotic anaesthetic in man.

LARGE DOSES OF MORPHINE ($0.5\text{--}3\text{ mg}\cdot\text{kg}^{-1}$) or fentanyl ($50\text{--}100\text{ }\mu\text{g}\cdot\text{kg}^{-1}$) produce complete anaesthesia and little change in circulatory dynamics during oxygen breathing.¹⁻³ Although anaesthetic doses of fentanyl cause fewer detrimental side effects than comparable doses of morphine, both techniques result in post-operative respiratory depression and other less significant but occasionally annoying problems; for example, morphine can stimulate histamine release and fentanyl may produce chest wall rigidity.³⁻⁸ A narcotic compound that is capable of producing complete anaesthesia with little or no alteration in circulatory dynamics and causing fewer side effects than either morphine or fentanyl would be an improvement as a narcotic anaesthetic. Recent work in our laboratories has demonstrated that alphaprodine (Nisentil), an old narcotic similar to but shorter lasting than meperidine and sulfentanil (N-[4-(methoxymethyl) 0-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxyl-1,2,3-propane tricarboxylate), a new synthetic narcotic which is shorter lasting and approximately ten times as potent as fentanyl, are capable of producing complete anaesthesia when administered intravenously in sufficient quantities (T.H. Stanley unpublished data). This study was designed to

investigate the cardiovascular effects of approximately equi-anaesthetic doses of each of these compounds in the dog.

METHODS

Thirty-one fasted mongrel dogs with an average weight of $19 \pm 2\text{ kg}$ served as the experimental subjects. Each animal had a large bore intravenous catheter placed in a foreleg vein. Anaesthesia was induced with thiopentone $15\text{--}20\text{ mg}\cdot\text{kg}^{-1}$ followed by succinylcholine $2\text{ mg}\cdot\text{kg}^{-1}$ intravenously. The trachea was intubated with a cuffed tube. The lungs were ventilated with pure oxygen* at a tidal volume of $8\text{--}12\text{ ml/kg}$ and a rate sufficient to maintain Pa_{CO_2} between $4\text{--}4.6\text{ kPa}$ ($30\text{--}35\text{ torr}$) as measured in aortic blood every $15\text{--}30$ minutes. A quadruple lumen Swan-Ganz catheter was placed in the pulmonary artery through the right internal jugular vein for determination of cardiac output ($\dot{Q}_T$) by the thermodilution technique and for measurement of mean pulmonary artery ($\overline{\text{PAP}}$), mean pulmonary capillary wedge (PCWP) and mean right atrial ($\overline{\text{RAP}}$) pressures. A second catheter was inserted into the aorta through the femoral artery and used for blood gas sampling and measurement of mean arterial blood pressure.

Fifteen dogs (eight in group 1A and seven in group 1B) received alphaprodine and 16 dogs

*Similar studies done with room air resulted in similar results after alphaprodine and sulfentanil; however, since previous studies from this and other laboratories have usually been reported during oxygen breathing, the latter data are reported in this manuscript.

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(eight in groups IIA and IIB) received sulfentanil. Dogs in the A groups received atropine 1.5 mg intramuscularly, 15–20 minutes before induction of anaesthesia. Dogs in the B group received no premedication. Fifteen minutes after completion of instrumentation, dogs in groups IA and IB were given alphaprodine at an infusion rate of $0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ which was increased after one hour to $0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and continued for 70 additional minutes. Dogs in groups IIA and IIB received an infusion of sulfentanil at a rate of $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ which was increased to $20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ after 30 minutes and to $40 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ after 60 minutes, continuing at this rate for an additional 70 minutes. Heart rate (HR), $\overline{\text{BP}}$, $\overline{\text{QT}}$, $\overline{\text{PAP}}$, $\overline{\text{PCWP}}$, $\overline{\text{RAP}}$, and pulmonary (PVR) and systemic vascular resistances (SVR) were measured before narcotic administration and 30, 60 and 90 minutes later. To determine the cardiovascular effects of nitrous oxide during infusion of alphaprodine and sulfentanil, all dogs were given 60 per cent nitrous oxide with oxygen to breathe after the 90-minute measurement and 15 minutes later 60 per cent nitrogen with oxygen. To determine the reversibility of each compound, naloxone 0.4 mg was given intravenously 15 minutes after breathing nitrogen. Cardiovascular dynamics were recorded 15 minutes after breathing nitrous oxide and nitrogen and five and ten minutes after naloxone.

Data were analyzed for statistical significance using Student's paired and unpaired t-tests.

RESULTS

All groups had similar arterial pH and oxygen and carbon dioxide tensions during the control period and showed no significant change in any of these variables during infusion of the narcotic compounds. All groups sustained significant but similar decreases in arterial oxygen tension during inhalation of nitrous oxide and nitrogen but no change in arterial pH or carbon dioxide tension.

Dogs in the A groups had significantly higher control (pre-narcotic infusion) HR and $\overline{\text{QT}}$ and lower SVR than dogs in the B groups. However, all other variables were similar in the two groups (Tables I and II). The only changes in this group during the remainder of the study were increases in PVR and SVR following addition of nitrous oxide and again after naloxone. Sulfentanil dogs without atropine (group IIB) sustained significant decreases in HR, $\overline{\text{BP}}$ and $\overline{\text{QT}}$ after 30 minutes but, like the atropinized group, had no further significant changes in these or any other variables

throughout the remainder of the study with the exception of SVR, which was increased following nitrous oxide and again after naloxone. Naloxone apparently did not reverse the anaesthetic state in any dog anaesthetized with sulfentanil.

Infusion of alphaprodine decreased HR, $\overline{\text{BP}}$, $\overline{\text{QT}}$ and SVR and increased PVR after 30 minutes but did not change $\overline{\text{PAP}}$, $\overline{\text{PCWP}}$, or $\overline{\text{RAP}}$ in groups IA and IB. Continued infusion of alphaprodine at $0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ or increasing the fusion to $0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ did not further influence any of these variables. Changing the inspired mixture of gases to 60 per cent nitrous oxide with oxygen increased $\overline{\text{BP}}$, $\overline{\text{PAP}}$, PVR and SVR and reduced $\overline{\text{QT}}$ but did not change any other variable in either group anaesthetized with alphaprodine. Breathing of 60 per cent nitrogen instead of nitrous oxide returned all variables to pre-nitrous oxide values. Administration of naloxone in groups IA and IB produced changes similar to nitrous oxide with the exception that $\overline{\text{QT}}$ was not changed. Naloxone reversed the anaesthetic effects of all dogs anaesthetized with alphaprodine, i.e., they all started to cough on their tracheal tubes, to open their eyes and to move about.

Groups IIA (atropine premedication, sulfentanil infusion) had significantly higher cardiac output throughout the pre-nitrous oxide period and higher blood pressure for the first 60 minutes of narcotic infusion than any of the other three groups ($p < 0.05$).

DISCUSSION

The results of this study demonstrate that anaesthetic doses of sulfentanil produce little changes in cardiovascular dynamics in atropinized dogs and only small decreases in HR, $\overline{\text{BP}}$ and $\overline{\text{QT}}$ in dogs without atropine premedication, irrespective of the infusion rate. In contrast, alphaprodine causes significant cardiovascular depression with or without atropine premedication. The data also indicate that, as with most narcotics, addition of nitrous oxide during alphaprodine infusion produces significant decreases in $\overline{\text{QT}}$ but increases systemic vascular resistance so that arterial blood pressure actually increases as well. On the other hand, addition of nitrous oxide during sulfentanil infusion, in contrast to most narcotics, has little influence on cardiovascular dynamics. Our findings suggest that large doses of sulfentanil deserve evaluation as a narcotic anaesthetic in man.

Advantages of high dose narcotic (morphine or fentanyl) and oxygen anaesthesia in man include

TABLE I
CARDIOVASCULAR DYNAMICS DURING INFUSION OF ALPHA-PRODINE AND SULEFENTANIL IN THE DOG (MEAN $\pm$ SD)

Narcotic	Group	Control	Mins of infusion				N ₂ O (60%) + O ₂	N ₂ (60%) + O ₂	Minutes after naloxone		
			30	60	90				5	10	
Heart rate (beats/min)	Alphaprodine IA	148 $\pm$ 8	115† $\pm$ 10	107† $\pm$ 10	106† $\pm$ 9	104 $\pm$ 11	106† $\pm$ 12	103† $\pm$ 10	108† $\pm$ 10		
	Alphaprodine IB	110 $\pm$ 9	99* $\pm$ 9	98* $\pm$ 8	95* $\pm$ 9	94* $\pm$ 10	95* $\pm$ 9	94* $\pm$ 10	96* $\pm$ 10		
	Sulfentanil IIA	136 $\pm$ 11	112† $\pm$ 13	104† $\pm$ 12	98† $\pm$ 15	99† $\pm$ 13	95† $\pm$ 11	92† $\pm$ 15	99† $\pm$ 13		
	Sulfentanil IIB	114 $\pm$ 9	89† $\pm$ 10	86† $\pm$ 12	78† $\pm$ 12	82† $\pm$ 13	84† $\pm$ 13	85† $\pm$ 11	88† $\pm$ 12		
Mean arterial blood pressure (kPa)	Alphaprodine IA	17 $\pm$ 1.4	14† $\pm$ 1.3	14† $\pm$ 1.3	15† $\pm$ 1.1	17 $\pm$ 1.1	15* $\pm$ 1.3	23† $\pm$ 2.1	22† $\pm$ 2.3		
	Alphaprodine IB	17 $\pm$ 1.5	12† $\pm$ 1.3	12† $\pm$ 1.4	13† $\pm$ 1.5	15† $\pm$ 1.3	13† $\pm$ 1.0	19* $\pm$ 1.1	20† $\pm$ 1.4		
	Sulfentanil IIA	17 $\pm$ 1.3	16 $\pm$ 1.1	16 $\pm$ 1.0	16 $\pm$ 1.1	17 $\pm$ 1.3	17 $\pm$ 1.1	17 $\pm$ 1.4	17 $\pm$ 1.1		
	Sulfentanil IIB	16 $\pm$ 1.4	14* $\pm$ 1.3	14* $\pm$ 1.7	15 $\pm$ 1.4	14* $\pm$ 1.1	14* $\pm$ 1.0	15* $\pm$ 1.0	15* $\pm$ 1.1		
Cardiac output (l/min)	Alphaprodine IA	2.9 $\pm$ 0.3	2.3† $\pm$ 0.2	2.3† $\pm$ 0.3	2.2† $\pm$ 0.3	1.7† $\pm$ 0.2	2.3† $\pm$ 0.3	2.1† $\pm$ 0.3	2.1† $\pm$ 0.3		
	Alphaprodine IB	2.0 $\pm$ 0.2	1.5† $\pm$ 0.2	1.4† $\pm$ 0.2	1.4† $\pm$ 0.2	1.2† $\pm$ 0.2	1.6† $\pm$ 0.2	1.5† $\pm$ 0.2	1.5† $\pm$ 0.2		
	Sulfentanil IIA	2.6 $\pm$ 0.3	2.6 $\pm$ 0.3	2.5 $\pm$ 0.2	2.4 $\pm$ 0.2	2.2 $\pm$ 0.2	2.5 $\pm$ 0.3	2.2 $\pm$ 0.3	2.3 $\pm$ 0.3		
	Sulfentanil IIB	2.0 $\pm$ 0.2	1.7* $\pm$ 0.2	1.6* $\pm$ 0.2	1.7* $\pm$ 0.2	1.6* $\pm$ 0.3	1.6* $\pm$ 0.3	1.6* $\pm$ 0.2	1.6* $\pm$ 0.3		

*P < 0.05, †P < .025, ‡P < .01, Students' paired t-test when compared to control values.

TABLE II
CARDIOVASCULAR DYNAMICS DURING INFUSION OF ALPHA-PRODINE AND SULFENTANIL IN THE DOG (MEAN $\pm$ SD)

Narcotic	Group	Control	Minutes of infusion				N ₂ O (60%) + O ₂	N ₂ (60%) + O ₂	Minutes after naloxone		
			30	60	90				5	10	
Mean pulmonary artery pressure (kPa)	Alpha-prodine IA	2.2 $\pm$ 0.2	2.1 $\pm$ 0.2	2.1 $\pm$ 0.2	2.1 $\pm$ 0.3	2.7* $\pm$ 0.2	2.1 $\pm$ 0.2	2.1 $\pm$ 0.2	3.4† $\pm$ 0.3	3.5† $\pm$ 0.3	
	Alpha-prodine IB	2.1 $\pm$ 0.2	2.1 $\pm$ 0.2	2.1 $\pm$ 0.2	2.1 $\pm$ 0.2	2.6* $\pm$ 0.2	2.2 $\pm$ 0.2	2.2 $\pm$ 0.2	3.3† $\pm$ 0.3	3.1† $\pm$ 0.3	
	Sulfentanil IIA	1.7 $\pm$ 0.2	1.7 $\pm$ 0.2	1.8 $\pm$ 0.2	1.8 $\pm$ 0.2	1.8 $\pm$ 0.2	1.8 $\pm$ 0.2	1.8 $\pm$ 0.2	1.8 $\pm$ 0.2	1.9 $\pm$ 0.3	
	Sulfentanil IIB	1.8 $\pm$ 0.2	1.7 $\pm$ 0.2	1.7 $\pm$ 0.2	1.7 $\pm$ 0.2	1.8 $\pm$ 0.2	1.9 $\pm$ 0.2	1.9 $\pm$ 0.2	2.1 $\pm$ 0.2	2.1 $\pm$ 0.2	
Systemic vascular resistance (dynes sec (cm ²))	Alpha-prodine IA	3701 $\pm$ 251	3083* $\pm$ 210	3031* $\pm$ 229	3105* $\pm$ 202	6704† $\pm$ 349	4002 $\pm$ 339	4002 $\pm$ 339	7167† $\pm$ 361	7080† $\pm$ 314	
	Alpha-prodine IB	5205 $\pm$ 310	3800* $\pm$ 271	4005* $\pm$ 298	4222* $\pm$ 306	6387† $\pm$ 372	4325* $\pm$ 341	4325* $\pm$ 341	7208† $\pm$ 291	7123† $\pm$ 335	
	Sulfentanil IIA	3426 $\pm$ 311	3064 $\pm$ 301	3172 $\pm$ 284	3993 $\pm$ 327	4679* $\pm$ 330	4008 $\pm$ 296	4008 $\pm$ 296	4917* $\pm$ 278	4932* $\pm$ 289	
	Sulfentanil IIB	4669 $\pm$ 269	4563 $\pm$ 300	4312 $\pm$ 254	4819 $\pm$ 307	5806* $\pm$ 313	4721 $\pm$ 327	4721 $\pm$ 327	5794* $\pm$ 348	5631* $\pm$ 315	
Pulmonary vascular resistance (dynes sec (cm ²))	Alpha-prodine IA	248 $\pm$ 19	327* $\pm$ 22	348* $\pm$ 21	354* $\pm$ 24	531† $\pm$ 27	392* $\pm$ 20	392* $\pm$ 20	534† $\pm$ 28	520† $\pm$ 32	
	Alpha-prodine IB	280 $\pm$ 18	358* $\pm$ 23	374* $\pm$ 21	368* $\pm$ 20	522† $\pm$ 25	380* $\pm$ 19	380* $\pm$ 19	550† $\pm$ 23	532† $\pm$ 24	
	Sulfentanil IIA	266 $\pm$ 19	268 $\pm$ 18	271 $\pm$ 18	309 $\pm$ 20	321* $\pm$ 21	308 $\pm$ 19	308 $\pm$ 19	347* $\pm$ 22	354* $\pm$ 23	
	Sulfentanil IIB	229 $\pm$ 17	273 $\pm$ 18	253 $\pm$ 21	264 $\pm$ 19	283 $\pm$ 19	266 $\pm$ 21	266 $\pm$ 21	297 $\pm$ 23	298 $\pm$ 24	

*p < 0.05, † < 0.01, Student's paired t-test when compared to control values.

profound analgesia and complete anaesthesia without significant alteration of cardiovascular dynamics.¹⁻⁶ Unfortunately, anaesthetic doses of morphine can result in increased blood or other colloid requirements during operation and post-operatively⁸ and prolonged (up to 36 hours) post-operative respiratory depression.⁷ Anaesthetic doses of fentanyl, while having fewer disadvantages than comparable doses of morphine,^{3,5} can occasionally result in chest wall rigidity on induction (usually caused by two rapid a fentanyl infusion rate)⁴ and may necessitate postoperative mechanical ventilation from two to eight hours after open heart or other major operations.^{3,5} A narcotic anaesthetic that possessed the advantages of fentanyl and morphine and which had less or none of the disadvantages could be extremely desirable, not only in patients with significant cardiovascular disease, but perhaps in all surgical patients.

In evaluating the possibilities of all currently available and newly developed opioids as potential narcotic anaesthetics, we considered that both alphaprodine (Nisentil) and sulfentanil might be desirable because of their relatively short duration of action.⁹⁻¹² Alphaprodine, while similar in structure to meperidine, has been described as having a duration of action that is markedly shorter than the latter.^{9,10} As a result, it has been a popular narcotic for pain relief in the labour room.¹³ Similarly, sulfentanil has been described as being shorter acting and more potent than fentanyl,¹¹⁻¹² two desirable traits in a new narcotic anaesthetic.

An important pre-clinical step in evaluating the potential of a narcotic as an anaesthetic is to determine the cardiovascular effects of anaesthetic doses of the compound in a basal anaesthetized dog. One group with and one without atropine are usually evaluated because many narcotics have profound stimulating properties on the central vagal nucleus, particularly in the dog but also in man, and produce marked decreases in heart rate which can alter cardiac output and other cardiovascular variables.^{3,14}

Although the doses of alphaprodine used in this study were anaesthetic (Reddy, P. unpublished data) and could be easily reversed with naloxone, unfortunately the compound produced significant decreases in arterial blood pressure, heart rate and cardiac output with or without atropine. While careful studies of the effects of alphaprodine on myocardial dynamics have not been done, it is likely, in view of the similarity of the structure of the compound to meperidine, which

is well known as severe myocardial depressant,¹⁵ that alphaprodine also produces direct myocardial depression. Unless additional studies yield advantages of alphaprodine over comparable doses of fentanyl it is unlikely that the former will be of much value as a narcotic anaesthetic in man.

In contrast to alphaprodine and similar to fentanyl,¹⁴ anaesthetic doses of sulfentanil result in little change in any cardiovascular variable except heart rate, in atropinized animals. Furthermore, changing the inspired mixture of gases to nitrous oxide in oxygen produced little additional change except increases in pulmonary and systemic vascular resistances. These changes are similar to those found when nitrous oxide is inhaled during infusions of fentanyl in the dog¹⁴ and in contrast to those reported when nitrous oxide is breathed during meperidine or morphine infusions.^{16,17} If similar findings occur in man, and if subsequent studies demonstrate that sulfentanil has a shorter duration of action in man, as it does in animals,^{11,12} sulfentanil with nitrous oxide or oxygen may become an important anaesthetic in patients with little circulatory reserve.

The cardiovascular changes produced by naloxone after alphaprodine in this study are not unexpected and have been reported by others.¹⁸ They confirm the potential danger of antagonizing a narcotic in patients who have ischaemic cardiac disease who cannot tolerate increase in heart rate and arterial blood pressure. The inability to antagonize the anaesthetic effect of sulfentanil with naloxone was unexpected. Naloxone readily antagonized the anaesthetic effects of comparable doses of alphaprodine in this study and has done the same with comparable doses of other narcotics including fentanyl (Stanley, T.H., unpublished data) in dogs, as well as in man. This finding is interesting in view of the reports that sulfentanil accumulates in central nervous system tissue to a lesser extent than fentanyl.¹¹ Perhaps sulfentanil binds more tightly than fentanyl and other narcotics to central nervous system opiate receptors and, therefore, requires greater doses of naloxone. On the other hand, sulfentanil may also interact with other than opiate central nervous system receptors. Whatever the explanation, additional studies will have to be undertaken to determine whether similar responses occur in man and, if so, whether they have any clinical implications.

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RÉSUMÉ

Les effets hémodynamiques de doses anesthésiques équivalentes d'alphaprodine et de sufentanil ont été étudiés chez le chien sous ventilation mécanique. On a également étudié les effets de l'association d'atropine à chacun des médicaments, ceux de l'inhalation d'un mélange de 60 per cent de protoxyde d'azote et d'oxygène, puis ceux de l'inhalation d'un mélange de 60 pour cent d'azote et d'oxygène, et enfin les effets de l'administration de naloxone.

Les résultats indiquent que des doses anesthésiques de sufentanil produisent peu de modifications hémodynamiques chez le chien atropinisé et des changements mineurs seulement chez le chien n'ayant pas reçu d'atropine, sans égard à la vitesse d'administration du sufentanil. D'autre part, l'alphaprodine produit une dépression cardiovasculaire significative, indépendamment de l'administration préalable d'atropine. La naloxone a renversé les effets anesthésiques chez tous les chiens anesthésiés à l'alphaprodine, mais n'a renversé cet état chez aucun des chiens ayant reçu du sufentanil.

Nos résultats suggèrent que le sufentanil mérite une évaluation clinique chez l'humain.