The Effects of Meperidine in the Pulmonary Vascular Bed of the Cat

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Objective: **The purpose of this study was to test the hypothesis that meperidine induces a dilator response in the feline pulmonary vascular bed, and to identify receptors involved in the mediation or modulation of these effects.**

Design: **Prospective vehicle controlled study.**

Setting: **University research laboratory.**

Subjects: **Intact chest preparation; adult mongrel cats.**

Interventions**: In separate experiments, the effects of diphenydramine (histamine H_1-receptor antagonist), glibenclamide (adenosine triphosphate–sensitive K+ channel blocker), L-N^5-(1-Iminoethyl) ornithine hydrochloride (L-NIO) (nitric oxide synthase inhibitor), naloxone (opioid receptor antagonist), and nimesulide (selective cyclooxygenase-2 inhibitor) were investigated on pulmonary arterial responses to meperidine and other agonists in the feline lung bed.**

Measurements and Main Results: **The systemic pressure and lobar arterial perfusion pressure were continuously monitored, electronically averaged, and permanently recorded. Under elevated tone conditions in the isolated left lower lobe vascular bed of the cat, meperidine induced a dose-dependent vasodilator response that was not significantly altered after administration of glibenclamide, L-NIO, and nimesulide. Responses to meperidine were significantly attenuated after the administration of diphenydramine and naloxone.**

Conclusions: **The results suggest that meperidine has potent vasodilator activity in the feline pulmonary vascular bed, and these responses are mediated or modulated, in part, by opioid and histamine receptor–sensitive pathways.**
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KEY WORDS: meperidine, opioid receptor, histamine receptor, vasodilator, pulmonary hypertension

FOR THE PURPOSE OF general anesthesia, individual drugs are rarely delivered as a sole medication because of their extensive profile of side effects with large doses including cardiopulmonary depression. Furthermore, general anesthetics may result in prolonged amnesia and sedation, may provide ineffective analgesia, and may not provide adequate muscle relaxation.[1] Thus, general anesthetics are often combined with adjuvant medications to lower the dosages of general anesthetics as well as to provide better perioperative management.[1] Many critical care and cardiothoracic patients are often provided with high-dose opioid techniques as a major portion of the anesthetic technique delivered.

The opioid meperidine exerts agonist activity roughly at one tenth the potency of morphine at the mu-receptor in the central nervous system. Thus, meperidine delivery provides dose-dependent analgesia, respiratory depression, pupillary constriction, increased sensitivity of the labyrinthine apparatus, and affects endocrine function.[1] Although the pharmacology of opioids such as meperidine has been investigated in the central nervous system, little, if anything, is known of the effects of meperidine in the lung vasculature. Previous studies have shown that opiate agents such as morphine increase plasma histamine levels, whereas fentanyl does not.[2] Meperidine has been shown to have direct effects on voltage-gated potassium channels in a patch clamp preparation, as well as direct uterine relaxant effects independent of opioid antagonists, nitric oxide synthase, or cyclooxygenase (COX) inhibitors.[3,4] Therefore, the present study was undertaken to investigate the pulmonary vascular response to meperidine in the pulmonary vascular bed of the closed chest cat under constant flow conditions.

METHODS AND MATERIALS

After approval by the institutional review board for the care of animal subjects and while maintaining standards of care and handling of the animals in accordance with National Institutes of Health guidelines, 27 adult mongrel cats of either sex weighing 3.0 to 4.7 kg were sedated with intramuscular ketamine hydrochloride (10-15 mg/kg) and anesthetized with intravenous (IV) pentobarbital sodium (30 mg/kg). The animals were restrained in the supine position on a fluoroscopic table, and supplemental doses of anesthetic were administered as necessary to maintain a uniform level of anesthesia. The trachea was intubated with a cuffed pediatric endotracheal tube, and the animals spontaneously breathed room air enriched with 100% O_2. Therefore, the O_2 concentration was approximately 40%. Systemic arterial pressure was measured from a catheter inserted into the aorta from a femoral artery. IV injections were given into a catheter positioned in the inferior vena cava from a femoral vein, and intra-arterial (IA) injections were given into the perfused lobar artery.

For perfusion of the left lower lobe of the lung, a triple-lumen 6F balloon perfusion catheter was passed under fluoroscopic guidance from an external jugular vein into the artery to the left lower lobe. After the animal had been heparinized (1,000 U/kg IV), the lobar artery was vascularly isolated by distension of the balloon cuff on the perfusion catheter. The lobe was perfused with a Harvard model 1210 perfusion pump (Harvard Apparatus, South Natick, MA) by way of the catheter lumen beyond the balloon cuff with blood withdrawn from a femoral artery. The perfusion rate was adjusted so that lobar arterial perfusion pressure approximated the mean pressure in the main pulmonary artery and was not changed thereafter. The flow rate ranged from 30 to 41 mL/min, and, in some experiments, left atrial pressure was measured with a radiopaque 6F single-lumen or 6F double-lumen catheter passed transseptally into the left atrium from an external jugular vein. All vascular pressures were measured with SpectroMed DTX Plus (Viggo-Spectromed, Oxnard, CA) transducers zeroed at the right atrial level and were recorded on a Grass model 7D recorder (Grass Instruments, Quincy, MA).

All agonists were injected directly into the lobar arterial perfusion

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circuit in small volumes and in random sequence. Sufficient time was permitted between injections for pressure to return to baseline values. Because lobar arterial perfusion flow is constant, alterations in lobar pressure would represent changes in pulmonary arterial vascular resistance.

The antagonists diphenydramine, a histamine H_1-receptor blocker; glibenclamide, an ATP-sensitive K+ channel blocker; L-N^5-(1-iminoethyl) ornithine hydrochloride (L-NIO), an inhibitor of nitric oxide synthase; naloxone, an opioid receptor antagonist; and nimesulide, a selective COX-2 inhibitor were dissolved in normal saline immediately before use. The agonists meperidine (4.0-40.0 μg), an opioid receptor agonist; bradykinin (0.2-0.5 μg), an inducer of nitric oxide synthase; and nitroglycerin (4.0-40.0 μg), a cyclic guanosine monophosphate inducer were also dissolved in normal saline immediately before use. Stock solutions of the thromboxane A_2 mimic U46619 (Upjohn, Kalamazoo, MI) were prepared in 100% ethanol at concentrations of 5 to 10 mg/mL and were stored in a freezer at −20°C. All vehicle solutions (agonist and antagonist) used produced no significant effect on lobar arterial pressure. Working solutions were prepared just before use, stored in brown-stoppered bottles, and kept on crushed ice during the experiments.

The pulmonary vascular bed of the intact cat has little, if any, vasopressor tone response under resting conditions when the F_IO_2 is 0.21. Therefore, pulmonary arterial pressure in the bed must be actively increased so that vasodilator responses can be expressed. In all experiments, tone was raised in the control period to an average value of 35 ± 2 mmHg with an intralobar infusion of U46619. Under conditions of increased tone in the control period, pulmonary vascular responses to meperidine, bradykinin, and nitroglycerin were obtained. The agonists were injected in small volumes directly into the perfusion circuit distal to the pump in a random sequence during the control period.

The experiments were divided into 5 groups. In the first set of experiments, responses to intralobar agonists were studied under elevated tone conditions. Before glibenclamide infusion, the thromboxane A2 mimic U46619 was stopped because of the potential for glibenclamide to increase tone, and lobar arterial pressure was permitted to return to near control values. After the peak increase in lobar arterial pressure in response to glibenclamide (5 mg/kg IA, n = 5), the thromboxane A2 mimic U46619 infusion was resumed if necessary to raise pulmonary vascular tone to a level similar to that attained during the control period. In some experiments, glibenclamide administration alone was sufficient to increase lobar vascular tone to a level equal to the control level. In these experiments, thromboxane A2 mimic U46619 infusion was resumed when lobar arterial pressure had decreased to <30 mmHg. Responses were compared before and beginning 20 to 30 minutes after administration of glibenclamide given intra-arterially.

In the second through fifth sets of experiments, the responses to intralobar agonists were measured after administration of diphenydramine (1.0 mg/kg IV, n = 5), L-NIO (1.0 mg/kg IV, n = 5), naloxone (0.1 mg/kg IV, n = 5), and nimesulide (3.0 mg/kg IV, n = 5). Responses were compared before and beginning 20 to 30 minutes after administration of diphenydramine, L-NIO, naloxone, and nimesulide given intravenously.

All vascular pressures are expressed in absolute units (mmHg) as means ± standard deviation (SD). The data were analyzed with a paired and unpaired *t* test and Scheffé's F test (Excel 2002, Microsoft, Redmond, WA). A value of $p < 0.05$ was considered the criterion for statistical significance.

RESULTS

The effects of diphenydramine on responses to meperidine and bradykinin are shown in Figure 1. At a dose that significantly attenuated the vasodilatory effects of meperidine, the vasodilator effects of bradykinin were not significantly altered after administration of diphenydramine (1.0 mg/kg IV). The effects of glibenclamide in response to meperidine are shown in

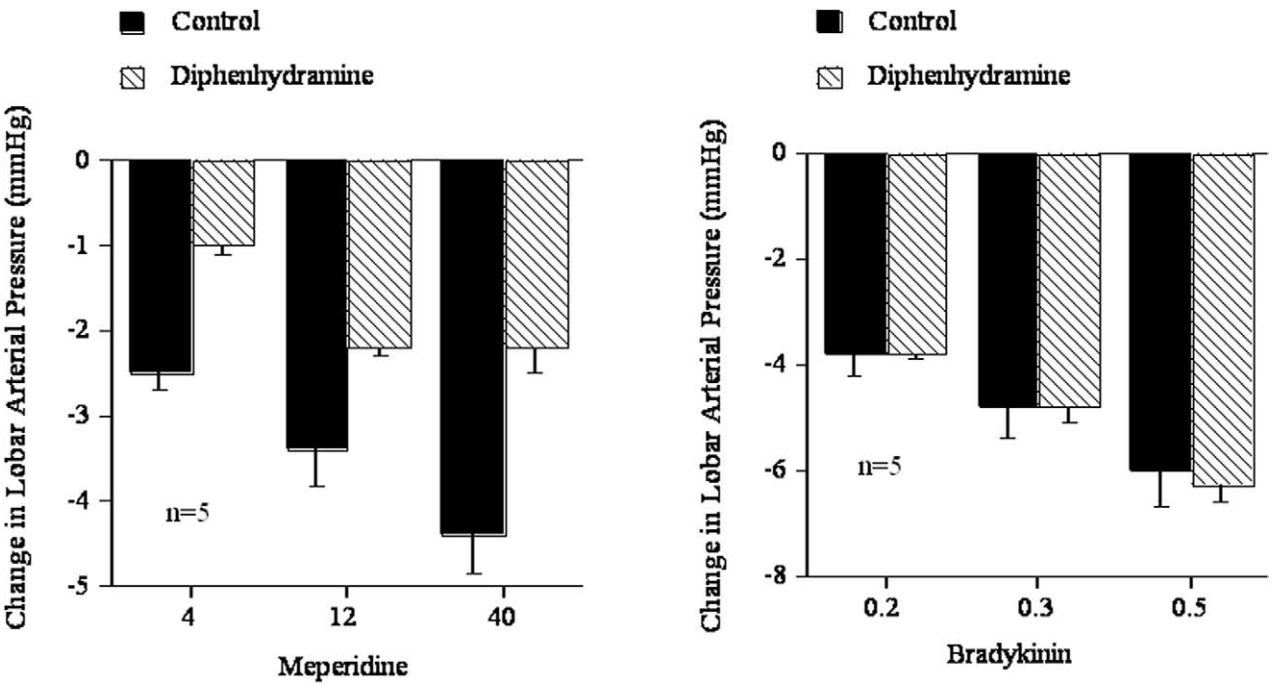

Fig 1. Influence of diphenydramine on responses to meperidine (n = 5) and bradykinin (n = 5). *$p < 0.05$. Data are expressed as mean ± SD.

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