Dose-Response of Intravenous Butorphanol to Increase Visceral Nociceptive Threshold in Dogs (43258)

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Abstract. **This study was designed to determine the effective analgesic dose of butorphanol administered intravenously to obtund visceral nociception, as well as to determine duration of this effect. Additionally, cardiovascular changes and sedative effects were defined. Eight healthy dogs were each given five doses of butorphanol (0.025, 0.05, 0.1, 0.2, and 0.4 mg/kg) plus a sterile water placebo intravenously in a randomized blinded format. Antinociception was assessed using an inflatable Silastic balloon inserted into the colon. Blood pressures and pulse rates were measured with a noninvasive monitor. The greatest efficacy and longest duration of antinociception were produced by 0.4 mg/kg of butorphanol, with a duration of 38 ± 9 min. Arterial blood pressure and pulse rate did not vary at antinociceptive doses. Mild sedation was observed at all doses, which generally lasted longer than the antinociceptive effects. These data suggest that butorphanol can be given alone intravenously to provide visceral antinociception lasting 30–45 min without significant side effects.** [P.S.E.B.M. 1991, Vol 197]

Butorphanol tartrate (Fort Dodge Laboratories, Fort Dodge, IA) is a synthetic opioid agonist-antagonist analgesic with a potency approximately five times that of morphine. It produces its effects by binding to opiate receptors and exerting little activity at some receptors and agonistic actions at others (1). Butorphanol has been demonstrated to be effective in relieving pain associated with colic in horses (2–4), in relieving pain in cats (5, 6), as an analgesic in humans (7), and as an antitussive in dogs (8). Clinical experience with butorphanol indicates that it has great potential as an effective analgesic in dogs (9). Butorphanol injected intravenously has been shown to induce small decreases in heart rate and arterial blood pressure in dogs (10). However, when given subcutaneously, no significant changes in heart rate or arterial blood pressure were recorded (11). There is no effect on respiratory rate for either subcutaneous or intravenous administration (10, 11). Dogs are reported to be mildly sedated after either intravenous or subcutaneous administration of butorphanol.

The major objective of this investigation was to determine the most effective analgesic dose of butorphanol given intravenously to obtund visceral antinociception in the dog. During the past 3 years, we have developed methods to measure responses to minimum-threshold visceral stimulation (12). The procedures used here were modifications of the techniques developed by Sawyer *et al.* (6, 12) and Dobkin *et al.* (7) in the cat, and Muir (13) and Pippi and Lumb (14) in the horse.

Materials and Methods

Research Subjects. One male and seven female neutered adult dogs of various breeds weighing 21.4 ± 0.9 kg were used in these studies, which were approved by the Michigan State University All-University Committee on Animal Facilities and Care. The subjects were housed in temperature- and humidity-controlled rooms holding four dogs each. Dogs were leash-walked outdoors twice daily and once on weekends. Each animal was also socialized and trained to become accustomed to the noninvasive monitoring devices. They received training at least twice each week and once on each day

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of study to lie in lateral recumbency without moving while fully instrumented.

Instrumentation. To assess the degree of antinociception, a specially designed Silastic catheter (Aire-Cuff; Bivona Inc., Gary, IN) with a 5- × 3-cm balloon attached (Fig. 1) was used for visceral nociceptor stimulation. One end of the catheter was rounded to facilitate insertion through the anus. The other end was tapered for a length of 25 cm to an opening where a stylet was inserted to help guide the balloon to the pelvic arch area of the colon. Once in place, the stylet was removed. Thick-walled plastic tubing (laboratory bubble tubing; Baxter Hospital Supply, Romulus, MI) was used to connect the balloon to a 1-gallon plastic bottle (Fig. 2). An inflation bulb was used to pressurize the bottle with room air. For each stimulus presentation, the volume of air was delivered to the balloon consistently in less than 0.5 sec by means of a three-way stopcock. Deflation of the balloon was accomplished by releasing the air pressure to the atmosphere using the same three-way stopcock. When inflated at threshold volumes, the balloon exerted a pressure (measured in mm Hg) on the visceral mucosa, which induced a minimum level of discomfort due to mild distention of the gut lumen (15). Changes in behavior indicating discomfort such as head-lift, altered posture, stretch hind-limb extension, or changes in ventilation subsequent to colonic balloon inflation were graded 1, 2, or 3: 1, unsure of the reaction; 2, a definite but minimum level of reaction; and 3, the greatest response with the pressure being released immediately (Table I). The evaluator was unaware of the level of pressure being exerted on the balloon for each stimulus presentation, this being adjusted by an assistant.

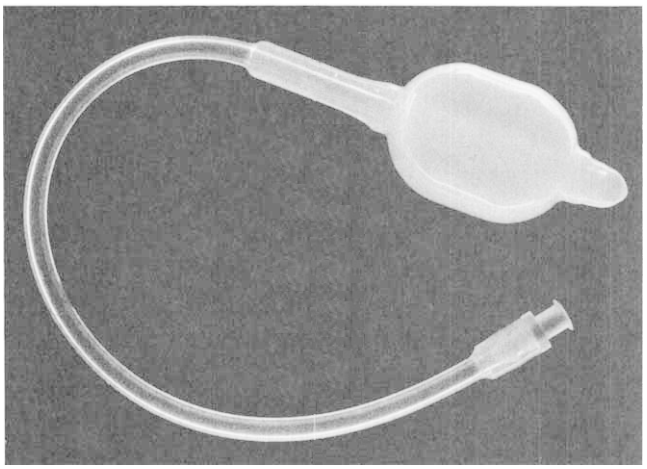

Figure 1. Silastic colon catheter.

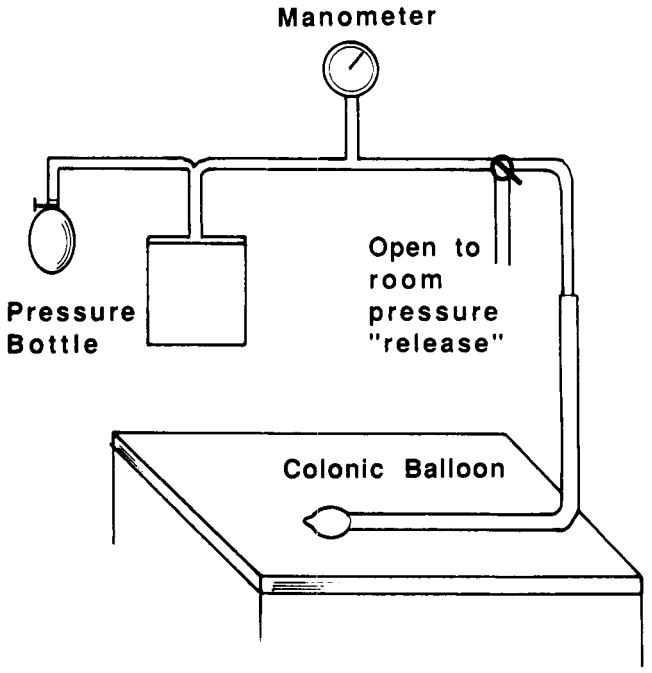

Figure 2. Colonic catheter inflation/deflation system.

Respiratory patterns were determined by recording chest movements associated with breathing using a mercury strain gauge connected to a plethysmograph (model 270-A; Parks Electronics, Aloha, OR). The strain gauge established one leg of a four-leg resistance element divider. Resistance imbalance of the bridge for different gauge lengths was transduced into a voltage signal that was recorded (Grass Polygraph model 5DWC12PA; Grass Instruments Co., Quincy, MA). The strain gauge was attached to a short piece of elastic mesh, which in turn was sewn to Velcro strips to make a "belt" placed around the dog's rib cage. This belt did not restrict the animal's normal respiratory movements and facilitated recording of both frequency and amplitude of the breathing pattern. Another body movement such as head-lift was also recorded by observing the disruption in the recorded breathing pattern.

A Dynamap Vital Signs noninvasive blood pressure monitor (1846 SX; Critikon Division of Johnson & Johnson, Tampa, FL) was connected to the forelimb using an external cuff. This device recorded systolic, diastolic, and mean arterial blood pressures and pulse rate.

Protocol. Studies were conducted on a 5-day/week

Table I. Criteria for Grading Sedation

0 =	None: No sedation.
1 =	Slight: Minimal, but detectable change in animal's awareness and interaction with the investigator, animal still responsive to environmental stimuli.
2 =	Moderate: Substantial change in animal's awareness and interaction with the investigator, sluggish response to environmental stimuli; dogs become recumbent and have difficulty standing.
3 =	Marked: Extreme depression, minimal response to environmental stimuli; dogs assume lateral recumbency, generally are unarousable and unable to ambulate, their eyes may be rotated downward.

schedule. Each dog was rested 7–8 days between studies. After a short training session on the day of study, each dog was instrumented with a strain gauge belt and a colonic balloon. The dog was then given a command to lie motionless on the table in lateral recumbency. Control measurements were taken for blood pressures, pulse rate, respiratory pattern, and minimum threshold stimulus/response to balloon inflation. This response level was verified at least twice to establish predrug control values.

Five doses of butorphanol (0.025, 0.05, 0.1, 0.2, and 0.4 mg/kg) plus an equivalent volume of sterile water (placebo) were administered intravenously to each dog in a randomized blinded manner following a Latin square design. Butorphanol tartrate (4 mg/ml, lot 87KO8V.25U) was provided by Fort Dodge Laboratories.

A 22-gauge × 1¼-in Teflon catheter (Cathlon IV; Critikon Division of Johnson & Johnson) was placed in a lateral saphenous vein, and an injection cap (Luer Lok; Becton-Dickinson Co., Rutherford, NJ) was attached. The catheter was flushed periodically with a small amount of heparinized saline and also after drug administration.

Blood pressures, pulse rate, respiratory patterns, and the minimum threshold stimulus/response level to colonic balloon pressure were determined at 15-min intervals after drug injection. Sedative effects induced by the drug were graded 0–3 following the criteria listed in Table I. These variables were also recorded at 15-min intervals throughout the duration of study.

After drug treatment, an increase in balloon pressure required to elicit behavioral response, which was above that eliciting the minimum threshold response during control measurements, was indicative of antinociception. Duration of antinociception was the time interval between injection of the drug and return to predrug control balloon pressure. Studies were continued until balloon pressures eliciting a minimum threshold response returned to control levels or for a minimum of 45 min and maximum of 240 min elapsed time.

Statistics. Regression analysis was done for doses versus balloon pressure to determine if increases in balloon pressure were related to dose. Furthermore, a curve-fitting program (curve fit-Jandel) was used to find the best relationship to fit the dose-response data. Analysis of variance for repeated measures and a multiple comparisons test (least significant difference) were used to determine significant differences ($P < 0.05$) in balloon pressure. Tukey's multiple comparisons test was used to determine significant differences ($P < 0.05$) in systolic, diastolic, and mean arterial pressures as well as pulse rate.

Results

As shown in Table II, there were no statistical differences between the predrug controls and the sterile water placebo. Results of regression analysis show a dose-related increase in balloon pressure over the range studied. However, the dose-effect relationship is not linear. Correlation coefficient values obtained using the curve-fitting software were 0.36 at the 15-min time point. Balloon pressure, expressed as a percentage of change from control for all doses and the placebo at 15 and 30 min postinjection (Fig. 3), indicate that all five doses provided antinociception. That is, all balloon pressures after a drug test were above predrug controls at the 15-min interval except for the placebo. At 30 min there were no significant differences from control for the four lowest doses. But balloon pressure at the 0.4-mg/kg dose was significantly different from placebo. At the 45-min period, mean balloon pressures had returned to or below predrug control levels, indicating no analgesia for any dose, although pressures were still quite high for several dogs.

Table II. Predrug Control Balloon Pressures for All Test-Dose Schedules[a]

Dog	mg/kg iv					
	Placebo	0.025	0.05	0.1	0.2	0.4
C	140	150	160	120	170	150
D	140	140	110	180	160	150
J	180	180	180	180	180	180
M	120	160	160	160	170	130
R	190	170	170	180	190	180
S	150	110	170	180	160	150
V	120	140	150	140	140	110
Z	150	130	130	150	90	150
Mean	149	147	154	161	157	150
SEM	8.9	7.9	8.2	8.1	10.9	8.2

[a] Units of pressure = mm Hg.

The longest mean duration of antinociception occurred at the 0.4-mg/kg dose with a mean time of 38 ± 9 min. However, due to large variabilities within each dose level, no statistical difference in duration of effect could be demonstrated between any of the doses tested.

Pulse rates at 15 and 30 min were not statistically different from predrug controls except at the 0.025-mg/kg dose, which decreased pulse rate from 87 ± 5 to 55 ± 2 at the 30-min interval (Fig. 4). However, the nociceptive response was not attenuated at this dose-time interval.

Systolic, diastolic, and mean blood pressures did not change after butorphanol injection at any of the doses tested (Fig. 5).

Mild sedation was observed at all doses. The highest level of sedation, with a mean score of 1.4, occurred at the 0.1-mg/kg dose at 15 min (Fig. 6A). Five dogs rated a score of 2 for sedation at 15 min, but at all other times sedation was graded less than 1. The degree of sedation did not correlate with the degree of antinociception (Fig. 6, B and C).

No discomfort or undesirable behavioral effects

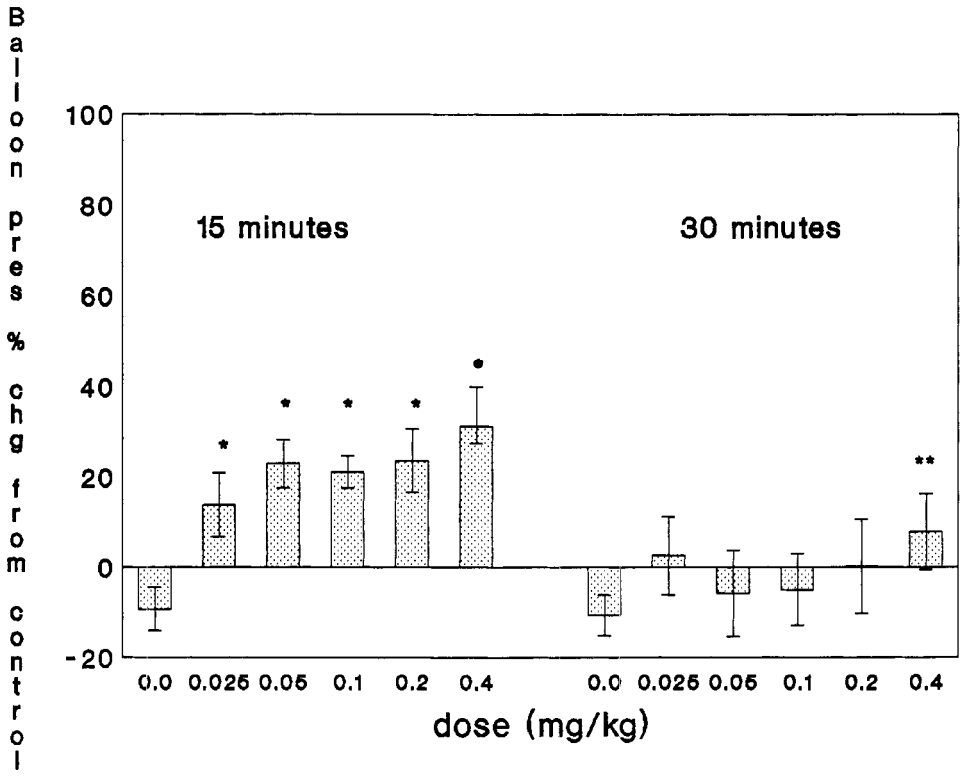

Figure 3. Magnitude of effect expressed as a percentage of change in balloon pressure from predrug control at 15 and 30 min postinjection of placebo and 0.025, 0.05, 0.1, 0.2, and 0.4 mg/kg of butorphanol, mean ± SE. *$P < 0.05$ relating to predrug control and placebo. **$P < 0.05$ compared with placebo.

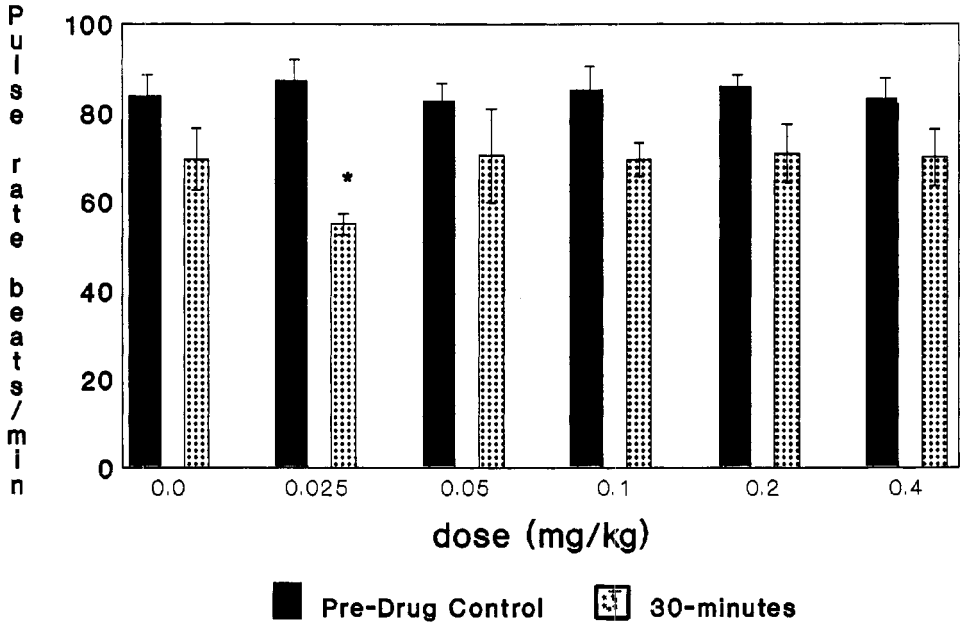

Figure 4. Pulse rates (beats/min) at the predrug control time period and 30 min after injection with placebo and 0.025, 0.05, 0.1, 0.2, and 0.4 mg/kg of butorphanol, mean ± SE. *$P < 0.05$ from predrug control.

that directly related to intravenous administration of any dose of butorphanol was observed in the subjects.

Discussion

The objective of this study was to determine the most effective antinociceptive dose of butorphanol administered intravenously in the dog. From previous investigations conducted in cats (7) and horses (4), it has been suggested that butorphanol produces a ceiling effect, with higher doses providing no more effective antinociception than lower doses. Analysis of the dose-response curve shows a similar ceiling effect in this

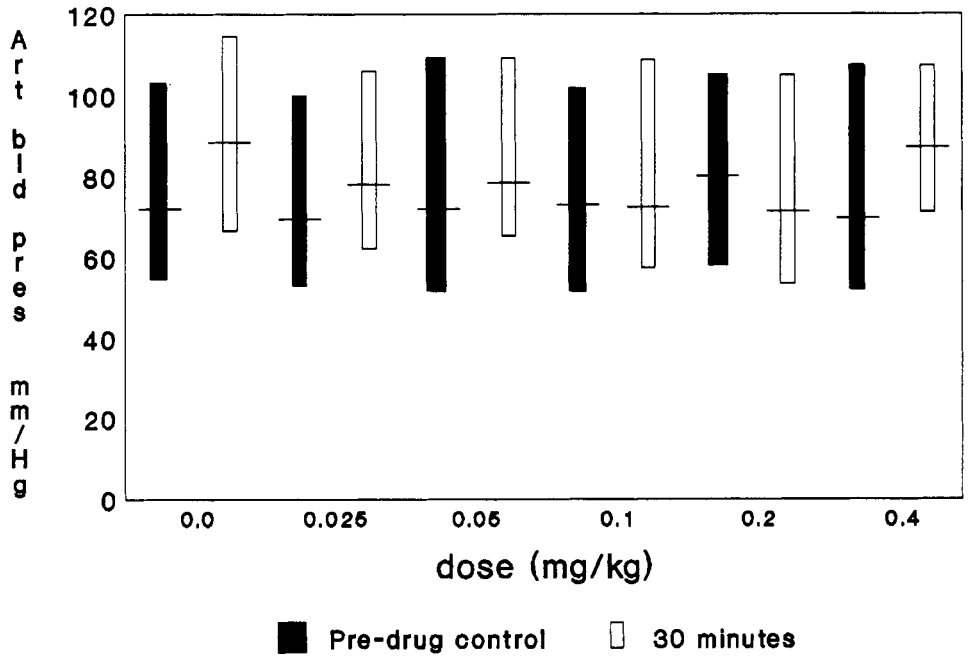

Figure 5. Systolic (top of bar), diastolic (bottom of bar), and mean (horizontal line on bar) arterial blood pressures at the predrug control time period and 30 min after injection with placebo (0.0) and 0.025, 0.05, 0.1, 0.2, and 0.4 mg/kg of butorphanol. All pressures are represented as mean values for all dogs.

study. The nonlinear curve was fit with a rectangular hyperbola, which reflects the rapid increase in response across low doses (0.025, 0.05, and 0.1 mg/kg) and a flat response across high doses (0.2 and 0.4 mg/kg). Furthermore, the lack of increased sedation with increasing dose is also suggestive of a ceiling effect in dose response.

In this study, 0.4 mg/kg produced the most significant change in nociception ($P < 0.001$) at 15 min. The same dose at 30 min was not different from control but did differ from the placebo ($P < 0.05$). These data suggest that butorphanol can be given intravenously to provide visceral analgesia for 15 to 30 min. The method we used for measuring visceral nociception is rather novel and has the advantage of being noninvasive. In addition, it has previously been applied to demonstrate comparable antinociceptive effects of both μ- and κ-opioid agonists in cats and rats (7, 12, 15). In these previous studies, a somatic nociceptive threshold (forepaw flinch to mild brief electric shock) was prominently increased by μ-agonists but not κ-agonists. This study demonstrates in dogs that a visceral nociceptive threshold is increased by butorphanol, a recognized κ-agonist (1). Based on the known sensory pattern associated with various stimuli to the intestinal wall of mammals (16), we consider that the balloon distention of the colon of these subjects induces a subjective response specifically of nociception. To our knowledge, other methods of assessing visceral analgesia have not been used in dogs. Otherwise, it would be interesting to compare the sensitivity of this method to other methods. However, by subjective observation of clinical canine patients, the dose response we used appears to have yielded a comparable effective dose (17, 18).

The duration of antinociception at all doses tested was relatively short, with duration ranging from 19 ± 5 min at 0.2 mg/kg to 38 ± 9 min at 0.4 mg/kg. Clinical impressions are that the analgesic effects of butorphanol exceed 1 hr (17, 18). The maximum duration of antinociception recorded was 75 min for one dog at the 0.4-mg/kg dose, and the mean duration for this dose was significantly different from all other doses. Differences in duration are not clear. The doses found to be effective in this study are consistent with those used in clinical practice, and perhaps the short duration of antinociception is the result of rapid hepatic metabolism of the drug when given intravenously (19). The mild sedative effects observed after administration of all doses of butorphanol were consistent with findings in published reports (9, 10). In the present study, the degree of sedation did not correlate with the degree of antinociception. When the dogs showed reduced responses to the visceral stimulus, mild sedation was present. However, antinociception terminated well before recovery from sedation. These observations suggest that the degree of sedation should not be used solely as a means of judging adequacy of analgesia.

Changes in pulse rate observed after administration of butorphanol were not significant except at the 0.025-mg/kg dose at 30 min. These results are not consistent with the findings of Trim (10), who reported significant decreases in heart rate in dogs after 0.1 mg/kg and 0.4

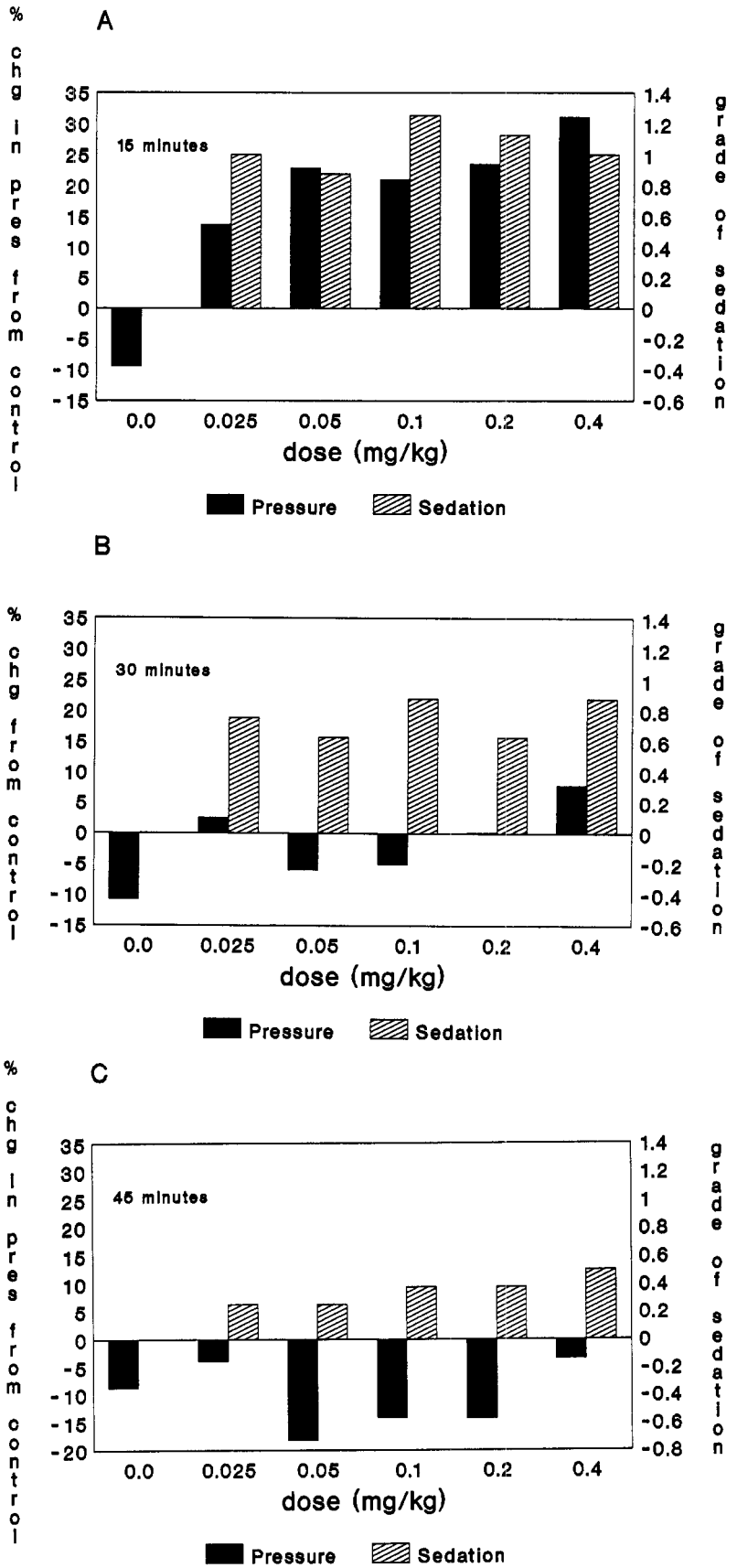

Figure 6. (A–C) Comparison between magnitude of effect (nociception) expressed as a percentage of change in balloon pressure from predrug control and grade of sedation at 15 min (A), 30 min (B), and 45 min (C) postinjection with 0.025, 0.05, 0.1, 0.2, and 0.4 mg/kg of butorphanol.

mg/kg of butorphanol given intravenously. However, our findings are consistent with those of Raffe and Lipowitz (11), who reported no significant changes in heart rate with butorphanol administered subcutaneously. These differences suggest that butorphanol should be given slowly intravenously, i.e., over 2 min, to avoid any possibility of bradycardia. There were no significant effects of butorphanol on arterial blood pressures at any dose tested. These findings also are not consistent with those of Trim (10), who found that 0.1 and 0.4 mg/kg of butorphanol given intravenously produced significant decreases in arterial blood pressure. Experimental conditions may have been different between these two studies, inasmuch as the dogs we used were well trained and accustomed to the noninvasive procedures. Baseline values for systolic and diastolic pressures for the dogs in Trim's (10) study ranged 45–70% higher than the baseline values for the dogs used in this study. However, these results are consistent with the findings of Raffe and Lipowitz (11), who reported no changes when the drug was given subcutaneously. Our results indicate that butorphanol, given slowly intravenously, has no effect on arterial blood pressures in healthy dogs at the doses tested, and we have verified the accuracy of the indirect blood pressure monitor used in this study (20).

Visceral antinociception with a duration of 38 ± 9 min results from intravenous administration of butorphanol at a dose of 0.4 mg/kg. It is likely that if a longer effect is desired, an equivalent dose can be given subcutaneously at the same time as the intravenous dose is administered.

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