Determination of a Sedative Dose and Influence of Droperidol and Midazolam on Cardiovascular Function in Pigs

Rosa Bustamante, and Alexander Valverde

ABSTRACT

Twelve pigs were randomly assigned to 1 of 2 groups, droperidol or midazolam, to determine a sedative dose of each drug that would facilitate handling of the pigs. Each pig in the group received all of the test doses with 5–7 d between treatments (droperidol-0.1, 0.3, 0.6 mg/kg, or midazolam-0.25, 0.5, 1.0 mg/kg) and saline (3 mL), IM. One investigator, unaware of the treatment administered, assessed the time of onset, degree, and duration of sedation. The 0.3 mg/kg dose of droperidol and 0.5 mg/kg dose of midazolam were judged to be the most suitable for sedation and produced similar degrees of sedation, although the onset and duration of sedation was significantly longer for the droperidol group. The effects of these 2 doses on heart rate, respiratory rate, systolic blood pressure, and rectal temperature were assessed in 12 pigs randomly assigned to 1 of the 2 treatments. Respiratory rate decreased significantly with droperidol at 10, 15, and 30 min. Temperature was significantly decreased at 60 min following midazolam. This study demonstrates that 0.3 mg/kg IM of droperidol and 0.5 mg/kg IM of midazolam induce adequate sedation in pigs with minimal cardiorespiratory changes.

RÉSUMÉ

Douze porcs furent répartis de façon aléatoire dans l'un des deux groupes de traitement suivants : dropéridol (DR), midazolame (MI), afin de déterminer la dose sédative de chaque médicament qui faciliterait la manipulation des animaux. Les porcs ont recu des doses de 0,1, 0,3, et 0,6 mg/kg de DR ou 0,25, 0,5, et 1 mg/kg de MI et 3 mL de saline en injections intra musculaire. De facon aveugle, le moment du début, la profondeur ainsi qui la durée de la sédation furent notés. La dose de 0,3 mg/kg de DR et de 0,5 mg/kg de MI furent jugées les plus appropriées pour leurs effets sédatifs quoique le moment du début et durée de sédation furent significativement plus longs pour le DR que pour le MI. Les effets de ces deux doses sur les fréquences cardiaque et respiratoire, sur la pression sanguine systolique et sur la température corporelle furent mesurés chez 12 porcs. Le DR a amené une diminution de la fréquence respiratoire à 10, 15 et 30 min après l'injection. La température corporelle a diminué après 60 min chez les animaux ayant recu le MI. Cette étude démontre que 0,3 mg/kg de DR et 0,5 mg/kg de MI induisent chez le porc une sédation adéquate sans changements cardiovasculaires importants.

(Traduit par docteur Pascal Dubreuil)

INTRODUCTION

Anesthetic management of pigs can be difficult due to their behaviour when physically restrained and the small vessels available for IV injections. Intramuscularly administered sedative drugs are preferred, and have included ketamine and xylazine, acepromazine, azaperone, diazepam, and droperidol/fentanyl (1–3). Some of these drugs can also produce adverse side effects on the cardiovascular and respiratory systems, such as bradycardia, tachycardia, hypotension, hypothermia, and respiratory depression (3).

Droperidol, a butyrophenone, has been used alone or in combination with fentanyl or meperidine to produce sedation in pigs since the late 1960's (4,5). Midazolam, a benzodiazepine, has also been recommended as a sedative in pigs (6). However, the sedative doses of these drugs have not been determined in controlled studies.

The aim of this study was to determine a sedative dose of droperidol and midazolam that will facilitate handling of pigs for diagnostic procedures, and the cardiorespiratory effects of the doses chosen.

MATERIALS AND METHODS

PHASE I

Twelve healthy mixed-breed pigs (8 females, 4 males), weighing 10–21 kg (16 ± 6.3 kg; mean ± SD), were used. Each animal was used on 4 occasions at 5–7 d intervals. Six of the animals (4 females, 2 males) received droperidol (Dehydrobenzperidol, Janssen Pharmaceutica, Belgium) at each of the test doses (0.1, 0.3, or 0.6 mg/kg) or 3 mL of physiological saline, into the thigh muscles (IM). The other 6 animals received midazolam (Dormicum, F. Hoffman-La Roche Ltd, Switzerland) at each test dose (0.25, 0.5, or 1.0 mg/kg) or 3 mL of physiological saline, IM. Assignment of animals to each of the groups and the order of test dose administration was random. Animals were handled according to the guidelines established by the National University of Costa Rica on animal care.

The degree of sedation was assessed by one of the investigators,

La Uruca Animal Hospital, P.O. Box 156-1000, San Jose, Costa Rica.

Address correspondence to Alexander Valverde.

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unaware of the treatment used, before administration of the treatment and at 3, 5, 10, 15, 30, and 60 min postadministration, using a scale from 0 to 3 (0 = no sedation; 1 = mild, responds to stimuli but allows handling; 2 = moderate, ataxia, ease of handling; and 3 = profound, recumbency, no response to stimuli). Stimuli included physical restraint, lifting, and encouraging the pig to walk. Time to onset of sedation (from a degree 0 to a degree ≥ 1) and duration of sedation (from a degree ≥ 1 to a degree 0) were recorded for each animal.

Data were analyzed using a one-way analysis of variance to compare the degree of sedation, time of onset and duration of sedation, produced by the test doses of each drug. The effective doses of each drug were compared using a one-way analysis of variance, with a $P < 0.05$ considered significant.

PHASE II

Twelve healthy pigs weighing 18–39 kg (26 ± 8.7 kg) were randomly divided into 2 groups. Group I (1 male, 5 females; 18–39 kg) were administered IM the dose of droperidol considered most effective in Phase I. Group II (4 males, 2 females; 18–29 kg) received the effective IM midazolam dose. Each animal was placed on a restraint table (6), and heart rate, respiratory rate, rectal temperature, systolic blood pressure, and an electrocardiogram were recorded before and at 3, 5, 10, 15, 30 and 60 min postadministration of each drug.

The heart rate and electrocardiogram were recorded using lead II (1500 B Electrocardiograph, Hewlett-Packard, Massachusetts, USA), respiratory rate was determined by observation, rectal temperature was determined with a rectal thermometer, and systolic blood pressure was determined by Doppler (Doppler 811-S, Parks Electronics Lab, Oregon, USA) using a cuff with a width of approximately 1/3 of the circumference of the forelimb at the level of the digital artery.

Data were analyzed using a one-way analysis of variance and a Tukey's procedure to determine at what times the parameters differed significantly. A $P < 0.05$ was considered significant.

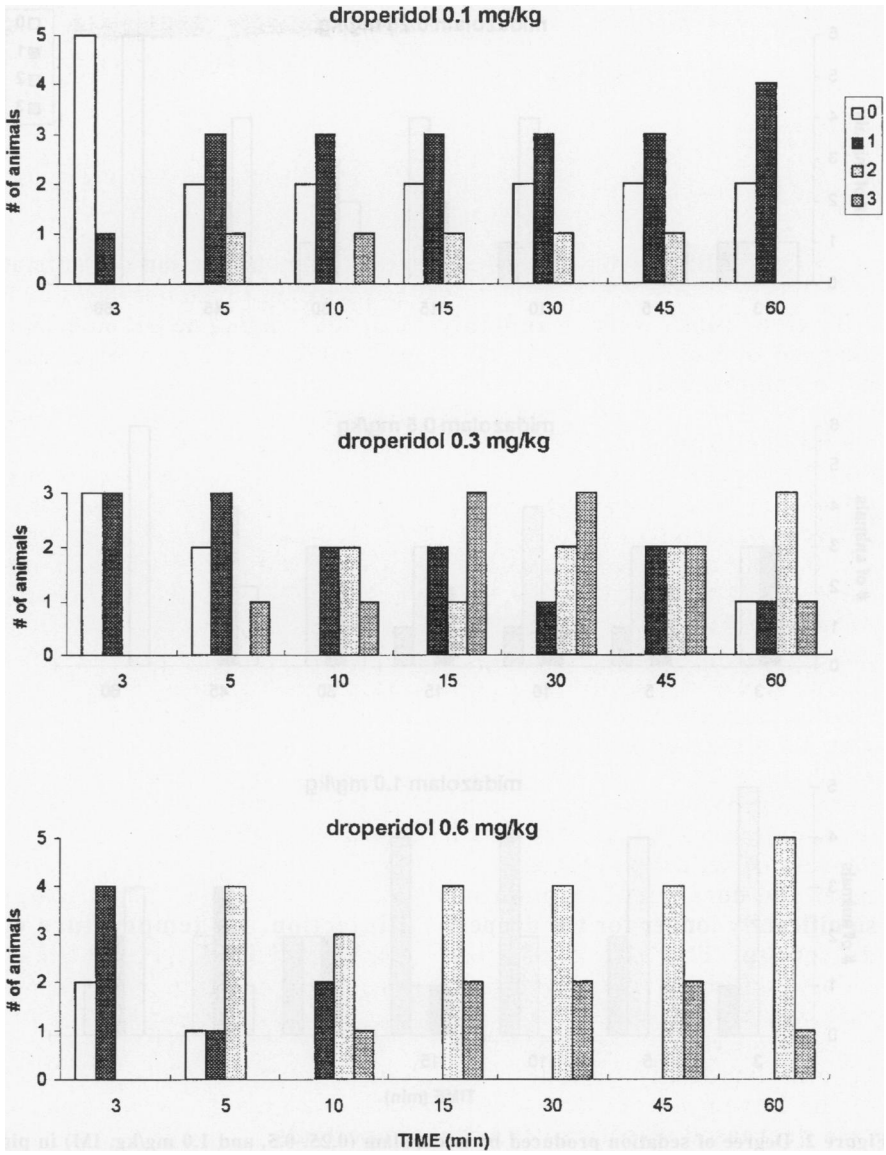

Figure 1. Degree of sedation produced by droperidol (0.1, 0.3, and 0.6 mg/kg, IM) in pigs. Response evaluated on a scale from 0 to 3, with 0 = no sedation; 1 = mild; 2 = moderate; and 3 = profound.

TABLE I. Time for onset and duration of sedation induced by IM droperidol (0.1, 0.3, 0.6 mg/kg) in pigs (n=6)

	Time (min)	
Dose	Onset of sedation	Duration of sedation
0.1 mg/kg	4.5 ± 1.00	84.3 ± 22.01[a]
0.3 mg/kg	5.2 ± 2.86	119.7 ± 51.13
0.6 mg/kg	4.3 ± 2.81	152.2 ± 33.08

Values are expressed as mean ± SD
[a] Significantly different ($P < 0.05$) from the 0.6 mg/kg dose

RESULTS

PHASE I

The 0.1 mg/kg dose of droperidol produced significantly less sedation ($P < 0.0001$) than the 0.3 mg/kg and 0.6 mg/kg dose at all time intervals (Figure I). The degree of sedation was predominantly moderate and profound with the intermediate and high dose. The onset of sedation was similar for all doses; however, the duration of sedation was significantly less for the low than for the high dose (Table I).

The 0.3 mg/kg dose was considered the most effective dose of droperidol

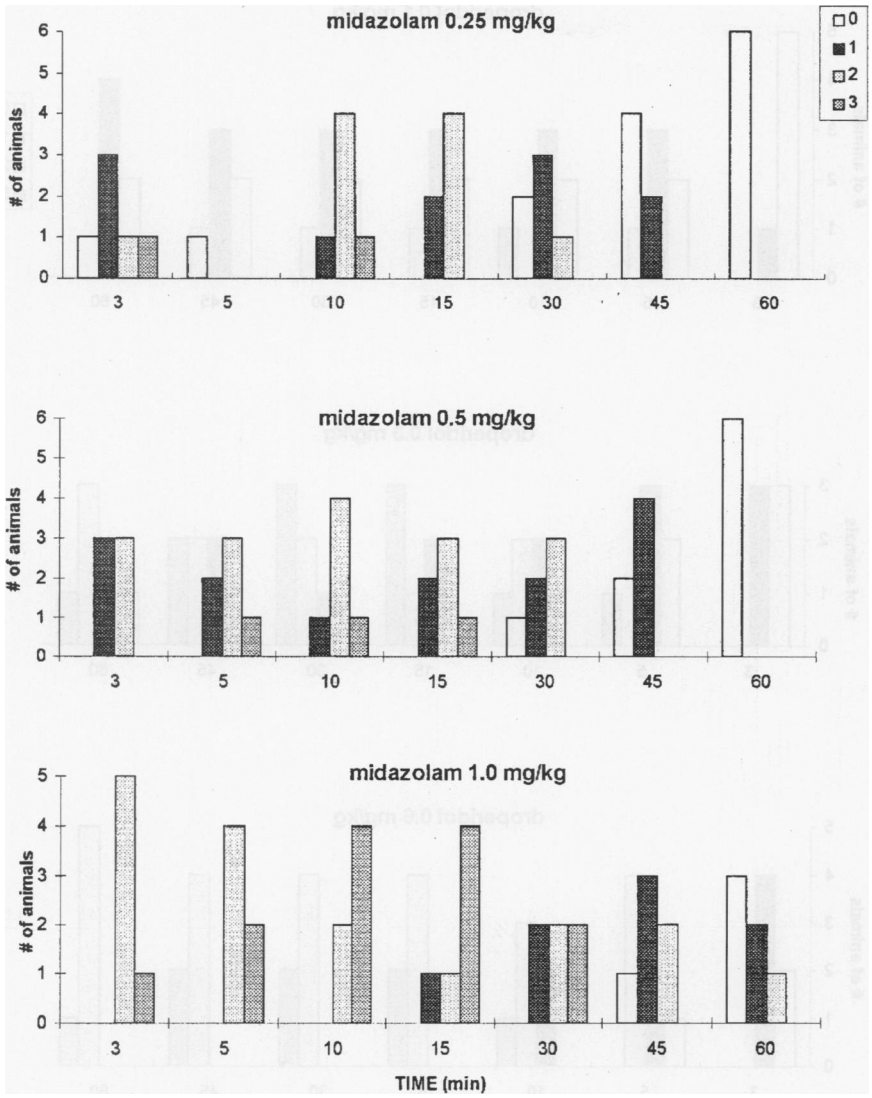

Figure 2. Degree of sedation produced by midazolam (0.25, 0.5, and 1.0 mg/kg, IM) in pigs. Response evaluated on a scale from 0 to 3, with 0 = no sedation; 1 = mild; 2 = moderate; and 3 = profound.

TABLE II. Time for onset and duration of sedation induced by IM midazolam (0.25, 0.5, 1.0 mg/kg) in pigs (n=6)

	Time (min)	
Dose	Onset of sedation	Duration of sedation
0.25 mg/kg	3.3 ± 3.33	41.8 ± 15.29[a]
0.5 mg/kg	2.0 ± 0.89	50.3 ± 12.94
1.0 mg/kg	1.5 ± 0.55	69.5 ± 24.73

Values are expressed as mean ± SD
[a] Significantly different ($P < 0.05$) from the 1.0 mg/kg dose

because the degree and duration of sedation induced were optimal for handling the pigs.

The 0.25 mg/kg and 0.5 mg/kg dose of midazolam produced significantly less sedation ($P < 0.0001$) than the 1.0 mg/kg dose at all time intervals (Figure II). The degree of sedation was dose related; all pigs exhibited a higher degree of sedation with higher doses. The onset of sedation was similar for all doses, and duration of sedation was significantly less for the low than for the high dose (Table II).

The 0.5 mg/kg dose was considered the most effective dose of midazolam for handling pigs.

The response to injection of the different treatments was similar for the droperidol and midazolam group, and was not associated with pain.

The sedative effects produced by the effective doses of droperidol and midazolam were statistically similar. However, the pigs administered droperidol were reluctant to move, whereas those administered midazolam exhibited an initial increase in motor and olfactory activity for approximately 5 min. Onset of sedation was significantly shorter for the midazolam than droperidol group (Tables I and II). Duration of sedation for the chosen doses was significantly longer ($P < 0.01$) for the droperidol than for the midazolam group (Tables I and II).

PHASE II

The 0.3 mg/kg dose of droperidol decreased respiratory rate significantly ($P < 0.007$) at 10, 15, and 30 min postadministration. Other variables remained unchanged (Table III).

The 0.5 mg/kg dose of midazolam decreased rectal temperature significantly ($P < 0.02$) at 60 min postadministration. There was no change in the other variables (Table IV).

DISCUSSION

Droperidol alone or in combination with fentanyl or meperidine has been used as a sedative in the pig (3–5). In general butyrophenones can induce extrapyramidal signs such as tremors, nystagmus, and rigidity in animals and human beings (7,8). The incidence in human beings is 1% (8). Its incidence in animals has not been reported, although defecation and object biting have been described in pigs (4,5). None of these behavioural changes were observed in this study.

In our study, the sedative effects of droperidol were evident within 5 min of administration, regardless of the dose administered. The degree and duration of sedation increased with higher doses. Sedation was optimal for handling at 15–45 min postadministration with the 0.3 mg/kg dose, although the duration of sedation lasted for approximately 2 h. Similarly, in another study using doses between 0.1 to 0.66 mg/kg, pigs administered the higher doses were more sedated (4). The effective dose

of droperidol determined in our study, 0.3 mg/kg, is within the recommended dose range of 0.1 to 0.4 mg/kg, described elsewhere (4). However, in our study, the individual response of each pig to the 3 test doses was determined, contrary to the previously reported study (4) where each pig received a single test dose of the 0.1 to 0.66 mg/kg range.

The benzodiazepines have anxiolytic, amnesic, anticonvulsant, hypnotic, sedative, and muscle relaxant properties (9). Diazepam has been the most commonly used benzodiazepine in pigs (3). The addition of organic solvents, like propylen glycol, to increase its solubility can cause pain on injection and venous thrombosis (10). In contrast, midazolam is water-soluble and does not cause pain on injection (9). In our study there were no differences in the response of pigs to the injection of droperidol, midazolam or saline.

The observed increase in motor activity, especially toward food searching, following midazolam administration, is in accordance with benzodiazepine's effects on appetite stimulation due to its direct effects on the appetite regulatory centre (11). Despite the increased motor activity, sedation was appropriate for handling the pigs, more so with the intermediate and high dose (0.5 mg/kg and 1.0 mg/kg, respectively). A dose of 0.1 mg/kg IM has also been reported to be adequate for sedation (6).

In our study, the sedative effects of midazolam were evident within 3 min postadministration and the maximum effect occurred at 15 min. It has been demonstrated that at physiological pH, midazolam becomes lipophilic and can be rapidly absorbed from the site of injection reaching the systemic circulation and crossing the blood brain barrier (8,9). Compared to droperidol, the sedative effects of midazolam had a shorter onset and duration of action.

The cardiovascular effects of droperidol include a hypotensive effect mediated through an ∝-adrenergic blocking effect (3,8). Hypotension did not occur in our study, since no changes were observed in systolic blood pressure with the 0.3 mg/kg dose. Other studies have demonstrated a decrease in mean blood pressure (12) and cardiac output (13) with the use of the butyrophenone, azaperone. There was, however, a vasodilatory effect of droperidol in this study, as evidenced by the engorgement of the auricular veins, similar to other studies with azaperone (14). This effect was not noted with the administration of midazolam.

TABLE III. Cardiorespiratory effects of intramuscular droperidol (0.3 mg/kg) in pigs (n=6)

		Time after administration (min)					
	Control	3	5	10	15	30	60
Heart rate (beats/min)	169 ± 22	174 ± 22	181 ± 16	180 ± 17	176 ± 13	169 ± 20	161 ± 25
Respiratory rate (breaths/min)	74 ± 19	69 ± 12	53 ± 18	47[a] ± 9	49[a] ± 10	46[a] ± 5	52 ± 21
Systolic pressure (mmHg)	156 ± 11	ND	153 ± 13	ND	154 ± 23	150 ± 25	152 ± 24
Temperature (°C)	39.9 ± 0.10	ND	ND	39.7 ± 0.26	ND	39.6 ± 0.42	39.5 ± 0.48

Values expressed as mean ± SD
[a] Significantly different ($P < 0.007$) from control
ND = not determined

TABLE IV. Cardiorespiratory effects of intramuscular midazolam (0.5 mg/kg) in pigs (n=6)

		Time after administration (min)					
	Control	3	5	10	15	30	60
Heart rate (beats/min)	166 ± 29	158 ± 16	157 ± 19	154 ± 18	149 ± 19	144 ± 12	150 ± 15
Respiratory rate (breaths/min)	65 ± 13	52 ± 26	45 ± 18	43 ± 17	39 ± 12	42 ± 17	45 ± 26
Systolic pressure (mmHg)	140 ± 8	ND	141 ± 9	ND	132 ± 15	129 ± 9	130 ± 8
Temperature (°C)	40.3 ± 0.43	ND	ND	40.0 ± 0.25	ND	39.8 ± 0.31	39.4[a] ± 0.64

Values expressed as mean ± SD
[a] Significantly different ($P < 0.002$) from control
ND = not determined

An antidysrhythmic effect of droperidol against adrenaline-induced arrhythmias has been reported (7,8). No dysrhythmias were observed in the present study. Heart rate remained unchanged after droperidol administration, similar to another study (5). In human beings, droperidol can induce an increase in heart rate (15), similarly, in horses azaperone can also induce a temporary tachycardia (16). Conversely, azaperone induces a decrease in heart rate in pigs (13).

The decrease in respiratory rate induced by droperidol coincided with the time when the maximum sedative effects of the drug were present. The positioning of the animal on the restraint table could have initially increased the respiratory rate, although enough time (approximately 30 min) was allowed for the pigs to acclimatize to the table and surroundings. It was not possible to measure arterial blood gases in this study, however, studies in human beings have not shown changes in arterial pCO_2 or pO_2 after droperidol administration (17,18).

The decrease in rectal temperature observed with droperidol was not statistically significant, but could be produced by the vasodilatory effects. Sedative doses of azaperone have also been shown to decrease body temperature in pigs (14).

Midazolam, similar to other benzodiazepines, causes minimal cardiorespiratory changes in animals and human beings (6,8). Incremental intravenous doses of 0.1 to 1.0 mg/kg administered hourly to pigs, produced a significant decrease in heart rate and respiratory rate, an increase in mean blood pressure and peripheral vascular resistance, whereas cardiac output,

pH and arterial blood gases were unchanged (6). The administration of 0.5 mg/kg in this study did not induce significant changes in respiratory rate, heart rate, and systolic blood pressure. The cumulative effects and intravenous administration of midazolam in the study by Smith et al (6) could account for their observed changes.

The decrease in rectal temperature, although statistically significant at 60 min, is not clinically relevant. Midazolam-induced hypotension can result in hypothermia in human beings (8,9). It is unlikely that this was the case in our study, since the systolic blood pressure remained unchanged.

Benzodiazepines decrease circulating noradrenaline and adrenaline plasma concentrations, preventing catecholamine-induced dysrhythmias (7,8). Similarly, no dysrhythmias were observed in this study.

In conclusion, the administration of 0.3 mg/kg of droperidol or 0.5 mg/kg of midazolam, IM, produces reliable sedation that facilitates handling of pigs, associated with minimal alterations in cardiovascular function and respiratory rate.

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