Comparison of Sedative Effects Induced by Medetomidine, Medetomidine-Midazolam and Medetomidine-Butorphanol in Dogs

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ABSTRACT. Sedative effects of combinations of medetomidine at 20 μg/kg - midazolam at 0.3 mg/kg (Me-Mi) and medetomidine at 20 μg/kg - butorphanol at 0.1 mg/kg (Me-B) were evaluated comparing with those of medetomidine alone (20, 40 and 80 μ/kg). All dogs given Me-Mi or Me-B were smoothly and rapidly induced to more profound and longer sedation than those by medetomidine alone. Especially, Me-Mi produced desirable sedation with moderate reflex depression, analgesia, excellent muscle relaxation and immobilization without further side effects. This potent effect of this combination seemed to be induced by a synergistic interaction between medetomidine and midazolam. This combination is available and valuable as a chemical restraint agent in dogs for various diagnostic or therapeutic procedures accompanied by light pain.—KEY WORDS: butorphanol, canine, medetomidine, midazolam, sedation.

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Medetomidine, 4-[1-(2,3-dimethylphenyl)ethyl]-1H imidazole hydrochloride, is a newly developed, highly receptor selective and potent α_2-adrenoceptor agonist [3]. Medetomidine produces deep sedation associated with muscle relaxation and analgesia through activation of α_2-adrenoceptors in the central nervous system [8, 25]. It has been reported that sedative effects induced by medetomidine is more profound than those by other known α_2-adrenoceptor agonists or other sedatives [25, 27]. The use of medetomidine as preanesthetic medication has also been reported to improve the anesthetic condition and reduce the requiring dose and undesirable effects of anesthetics [2, 9, 13]. Sedative effects induced by medetomidine can be reversed effectively and quickly by an α_2-adrenoceptor antagonist atipamezole [23, 26]. For these favorable properties, medetomidine has recently been of great interest as a drug of choice in veterinary anesthesia.

Recently, it has been reported that medetomidine with other tranquilizers or analgesics exerts more profound sedation than medetomidine alone [1, 4]. Midazolam, 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo (1, 5a) (1, 4), is a water-soluble benzodiazepine derivative and short acting tranquilizer. Like other benzodiazepines, midazolam has minimal cardiopulmonary depression [14]. When used alone, midazolam does not induce apparent sedation in dogs, however it enhances the effects of other anesthetics or sedatives [6, 21, 29]. A combination of medetomidine and midazolam has been reported to exert a synergistic effect in rats [17] and to induce deep sedation in humans and pigs [10, 19], while reducing the dose of medetomidine. Butorphanol, (−)-17-(cyclobutylmethyl) morphine-3,14-diol D-(−)-tartrate, is a synthetic opioid agonist-antagonist analgesic and exerts more potent effects than morphine, meperidine or pentazocine [12]. Although butorphanol has a weak or no sedative effect, it enhances the effect of α_2-adrenoceptor agonists such as medetomidine [16] or xylazine [15] as well.

Considering these properties, both combinations of medetomidine-midazolam and medetomidine-butorphanol are expected to exert more potent sedative effects than that by medetomidine alone. If some synergistic interaction can be expected between drugs of the combination, it will be much more desirable. To our knowledge, the sedative effects of medetomidine-midazolam, medetomidine-butorphanol and medetomidine alone have not been compared in dogs. The purpose of this study is to evaluate the sedative, analgesic and muscle relaxative effects produced by relatively low doses of medetomidine-midazolam and medetomidine-butorphanol combinations comparing with those by medetomidine alone in dogs.

MATERIALS AND METHODS

Animals: Thirty-one beagles in good health, 13 females and 18 males, 9.5 kg (range 7.2 to 15.8 kg) of average body weight and 14.0 months (range 8 to 30 months) of average age, were used in this study. Whenever different experiments were performed with the same dog, more than 7 days elapsed between experiments. The same dog was not used more than once in the same experiment group. Food was withheld at least 12 hr before the experiments, but animals were allowed free access to water.

Experimental protocol: Experiments were performed in a quiet room. After all base-line values of heart rate, respiratory rate and body temperature were obtained, 20 μg/kg of medetomidine (Domitor: Farmos Group Ltd., Finland) (Me20), 40 μg/kg of medetomidine (Me40), 80 μg/kg of medetomidine (Me80), 20 μg/kg of medetomidine and 0.3 mg/kg of midazolam (Dormicum: Yama-

nouchi Pharmaceutical, Japan) (Me-Mi) or 20 μg/kg of medetomidine and 0.1 mg/kg of butorphanol (Stadol: Bristol-Myers Squibb K. K., Japan) (Me-B) were administered in separate experiments (n=7 each). Medetomidine, medetomidine-midazolam or medetomidine-butorphanol mixed in the same syringe were injected intramuscularly in the hind limb. Drug doses for the combinations were tested in a preliminary investigation to establish dose combinations for adequate sedation.

Assessment of sedative, analgesic and muscle relaxative effects: Effects of each dose of medetomidine alone, medetomidine-midazolam and medetomidine-butorphanol were assessed by sedative, analgesic and muscle relaxant characters and by induction time (time from administration to lateral recumbency), arousal time (time from administration to sternal recumbency), recovery time (time from administration to total recovery from sedation) and duration of lateral recumbency. These effects were repeatedly assessed before, and (5), 10, (15), 20, 30, 40, 50, 60, 80, 100 and 120 min after drug administration or until complete recovery from sedation.

Sedative effect of each drug or drug combination was evaluated from posture, response to sound and depressions of swallowing and pedal reflexes. Posture and response to sound (three hand claps) were evaluated according to the following criteria; posture, score 0: normal, score 1: sedated but able to stand, score 2: sternal recumbency, score 3: lateral recumbency with apparent spontaneous movement (head and/or limb), score 4: lateral recumbency with subtle spontaneous movement (twitching and/or blink), score 5: lateral recumbency without spontaneous movement; response to sound, score 0: normal, score 1: decreased, score 2: slight, score 3: no response. Effects on swallowing and pedal reflexes were evaluated according to the following criteria; score 0: normal, score 1: weak, score 2: reflex (response) could be induced only by an increased stimulus, score 3: absent. Analgesic effects were evaluated by response to nose clamping, which was scored as described for assessment of reflexes. Muscle relaxant effects were estimated by observing jaw tone, which was scored according to the following criteria; score 0: resistant to opening mouth (difficult to open), score 1: moderately resistant to opening mouth (possible to open), score 2: slightly resistant to opening mouth (relaxed), score 3: not resistant to opening mouth.

Pattern and depth of respiration, mucous membranes, eyeball position, salivation, twitching and spontaneous movement were also recorded during sedation and side effects were noted whenever they occurred.

Heart rate (HR), respiratory rate (RR) and body temperature (BT) were measured before drug administration. HR was monitored by an electrocardiogram (ECG) (OEC-6301, Nihon Kohden, Japan) or a stethoscope, RR by observation and BT (rectal temperature) by a thermometer (model CTM-303, Terumo, Japan). These three measurements were repeated 5, 10, 15, 20, 30, 40, 50, 60, 80, 100 and 120 min after drug administration.

Statistical analyses: Statistical analysis of the results was performed as follows. Time interval data were analyzed by one-way analysis of variance and Duncan's multiple comparison procedure. The values of HR, RR and RT were analyzed by one-way analysis of variance, Shceffe's multiple comparison procedure (among the groups tested), and by two-way analysis of variance and Sceffe's multiple comparison procedure (*vs.* base-line values). P values below 0.05 were indicated as statistically significant.

RESULTS

Following administration of Me-Mi or Me-B, dogs were smoothly and rapidly induced to sedation. They were ataxic and drowsy within a few minutes and laterally recumbent in significantly shorter induction time than dogs given Me20 and Me40, and shorter than Me80 with no significance (Table 1). After being laterally recumbent, sedative condition in dogs given these combinations deepened further and reached to the maximal level approximately within 20 min. Considerable variation in condition of induction was found between dogs given medetomidine alone.

During being in maximal sedation for approximately 40 min, excellent immobilization was observed in dogs given Me-Mi and Me-B and they kept lateral recumbency without spontaneous movement (Fig. 1a) and became unconscious to the environment with eyes rotating down and no blink. In this phase, the animals did not respond to the environment and sound with moderate depression of reflexes (Figs. 1b, c and d). In dogs given Me-Mi, the scores for jaw tone (Fig. 1e) and response to nose clamping (Fig. 1f) were maintained higher values than those in dogs given Me-B or medetomidine alone, which indicated excellent muscle relaxation and moderate analgesia.

Sedation induced by medetomidine alone was deepened in the dose dependent manner. However, those dogs showed subtle spontaneous movements and responded to sound even at the highest dose (Me80) (Figs. 1a and b)

Table 1. Induction time, arousal time, recovery time and duration of lateral recumbency in dogs given medetomidine 20 μg/kg (Me20), 40 μg/kg (Me40), 80 μg/kg (Me80), medetomidine-midazolam (Me-Mi) and medetomidine-butorphanol (Me-B)[a)]

Drugs	Induction time (min)	Arousal time (min)	Recovery time (min)	Duration of lateral recumbency (min)
Me20	14.0±7.5^{A}	46.7±22.7^{A}	136.4±47.8^{A}	32.7±26.0^{A}
Me40	14.7±7.2^{A}	83.7±11.8 ^{B}	232.9±18.9 ^{BC}	69.0±17.0 ^{B}
Me80	12.6±5.2^{AB}	110.7±33.2 ^{C}	268.6±31.3 ^{B}	98.1±32.2 ^{C}
Me-Mi	6.7±2.6 ^{B}	96.4±18.9 ^{BC}	162.1±36.5^{A} ^{D}	89.7±18.8 ^{BC}
Me-B	6.9±3.9 ^{B}	99.0±19.6 ^{BC}	194.3±34.0 ^{CD}	92.1±20.9 ^{BC}

a) Data are expressed as mean±standard deviation.
A, B, C, D: Mean values with same superscripts are not significantly different (P>0.05).

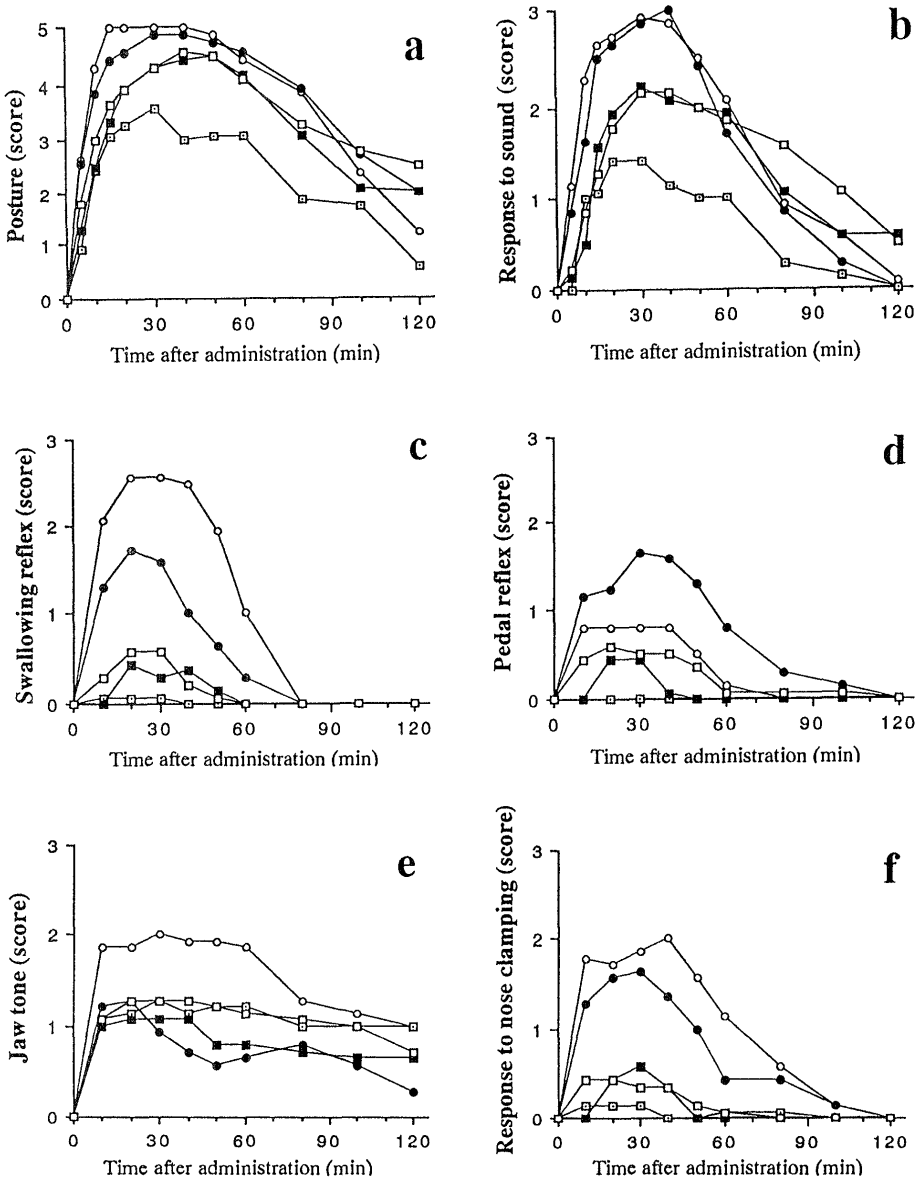

Fig. 1. Effects of 20 μg/kg of medetomidine (⊡), 40 μg/kg of medetomidine (■), 80 μg/kg of medetomidine (□), 20 μg/kg of medetomidine and 0.3 mg/kg of midazolam (○), and 20 μg/kg of medetomidine and 0.1 mg/kg of butorphanol (●) on posture (a) (full marks = 5), response to sound (b), swallowing reflex (c), pedal reflex (d), jaw tone (e), and response to nose clamping (f) (full marks = 3). Each symbol represents the mean value.

and sound stimuli often caused temporary arousal. Depression of reflexes and analgesia to nose clamping was hardly observed in these groups (Figs. 1c, d, f). In addition, three dogs given Me20 and two dogs given Me40 and one dog given Me80 were not induced to satisfactory sedation, responding the environment and changing their posture.

Mean duration of lateral recumbency of Me-Mi and Me-B were significantly longer than that of Me20, and longer than that of Me40 with no significance (Table 1). Initial arousal signs in all dogs were characterized by blink, recovery of eyeball to normal position and/or increased twitching. Then, head lifting and limb struggling appeared with clearer response to the environment. Recovery condition was smooth without excitement nor relapses to deep sedation in all groups. After arousal, all dogs given Me40 and Me80 remained moderately sedated and kept sternal recumbency for longer period than other dogs. Total recovery time of Me40 and Me80 were significantly longer than that of Me20 and Me-Mi (Table 1).

HR markedly decreased soon after drug administration, and remained the levels significantly below base-line values throughout the experiment in all groups with average values of 40–60 beats/min (Table 2). ECG revealed profound bradycardia with sinus arrhythmia. The

Table 2. Changes in heart rate, respiratory rate and body temperature after administration of medetomidine at 20 μg/kg (Me20), medetomidine at 40 μg/kg (Me40), medetomidine at 80 μg/kg (Me 80) medetomidine-middayolam (Me-Mi) and medetomidine-butorphand (Me-B)[a)]

		Time after administration (min)					
		Base-line	5	10	30	60	120
Heart rate (beats/min)	Me20	88.0±22.1^{A}	55.9±16.9^{*A}	48.1±13.1^{*A}	41.7±10.1^{*AB}	42.4±9.1^{*A}	58.6±13.9^{*A}
	Me40	87.3±11.7^{A}	45.0±10.5^{*A}	38.3±7.6^{*A}	34.0±5.0^{*A}	34.3±3.4^{*A}	38.0±6.0^{*B}
	Me80	98.0±19.7^{A}	42.0±8.9^{*A}	39.6±9.2^{*A}	37.0±5.5^{*AB}	41.1±5.0^{*A}	40.0±7.3^{*B}
	Me-Mi	93.9±19.3^{A}	54.6±8.7^{*A}	52.1±10.2^{*A}	51.1±8.5^{*B}	46.4±7.9^{*A}	52.1±13.7^{*AB}
	Me-B	88.3±26.4^{A}	52.9±10.0^{*A}	45.0±11.9^{*A}	43.1±11.4^{*AB}	44.4±9.5^{*A}	46.7±11.6^{*AB}
Respiratory rate (breaths/min)	Me20	16.6±3.0^{A}	15.7±5.6^{AB}	14.6±4.7^{A}	10.9±3.2^{*A}	10.1±1.9^{*A}	12.0±1.4^{A}
	Me40	24.6±10.2^{A}	19.1±7.9^{AB}	15.9±4.7^{AB}	11.6±2.8^{*A}	10.6±2.9^{*A}	12.3±2.9^{*AB}
	Me80	27.7±5.1^{A}	16.0±3.3^{*AB}	16.3±2.4^{AB}	10.7±4.4^{*A}	9.1±2.5^{*A}	10.3±1.8^{*A}
	Me-Mi	25.4±7.2^{A}	21.4±1.9^{B}	20.9±2.5^{B}	18.9±2.0^{B}	17.4±1.9^{*B}	16.9±2.8^{*B}
	Me-B	18.9±6.3^{A}	11.4±3.0^{*A}	11.4±1.9^{*A}	9.3±3.0^{*A}	8.6±2.8^{*A}	10.0±3.3^{*A}
Body temperature (°C)	Me20	38.7±0.4^{A}	38.7±0.5^{A}	38.7±0.5^{A}	38.5±0.4^{A}	37.5±0.7^{*A}	36.8±0.6^{*A}
	Me40	38.7±0.3^{A}	38.8±0.3^{A}	38.9±0.3^{A}	38.6±0.5^{A}	37.9±0.6^{*A}	36.8±0.6^{*A}
	Me80	39.1±0.4^{A}	39.4±0.4^{*A}	39.4±0.4^{*A}	39.1±0.5^{A}	38.2±0.5^{*A}	36.5±0.6^{*A}
	Me-Mi	39.2±0.4^{A}	39.2±0.4^{A}	39.2±0.5^{A}	38.9±0.6^{A}	38.1±0.6^{*A}	37.0±0.7^{*A}
	Me-B	38.7±0.5^{A}	38.8±0.6^{A}	38.7±0.7^{A}	38.2±0.9^{A}	37.3±0.9^{*A}	36.3±0.8^{*A}

a) Data are shown as mean±standard deviation (n=7 each).
*Significantly different from base-line value ($p<0.05$).
AB: Mean values with same alphabet are not significantly different ($p>0.05$).

bradycardia was also observed even in slightly sedated dogs given Me20. HR in Me-Mi tended to maintain higher level than those in Me40 and Me80, however a significant difference was observed only at 30 min after drug administration between Me-Mi and Me40. Even after the arousal, HR remained lower levels in all groups. RR decreased markedly after onset of sedation in all groups, however RR in Me-Mi maintained significantly higher level than those in other groups. In Me20, Me40, Me80, and Me-B, an irregular respiratory pattern with 15–30 sec of apnea followed by several rapid breaths was observed. Such an irregular respiratory pattern was not observed in Me-Mi. BT gradually decreased after administration in Me20, Me-Mi and Me-B. Although BT in Me40 and Me80 initially increased and then decreased thereafter, there were no significant differences among the groups tested.

Twitching was observed in all dogs given Me20 and Me40, four dogs given Me80 and two dogs given Me-B, whereas it was not observed in Me-Mi during the sedation. Two dogs given Me20 and Me40, one dog given Me80 and three dogs given Me-Mi vomited before onset of sedation. However, no vomiting was observed in the dogs given Me-B.

DISCUSSION

In this study, the combinations of medetomidine-midazolam and medetomidine-butorphanol exerted more potent sedative effects than any doses of medetomidine alone, enabling reduction of dose of medetomidine. Previous studies in dogs have reported that the recommended dose of medetomidine ranges from 10 to 80 μg/kg [25]. Among the doses, intramuscular injection of 40 μg/kg of medetomidine is widely recommended to produce adequate sedation appropriate for a range of clinical examinations and procedures in dogs [7, 24, 28]. However, cardiovascular depression can not be disregarded, considerable variation in sedation is found between animals, and some animals are not sufficiently immobilized and are possibly aroused by an external stimulus with this dose [4, 27, 28]. Medetomidine at 80 μg/kg (i.m.) induces longer sedation, however depressant effects on cardiovascular system and other undesirable effects are more profound than those by a lower dose of medetomidine [25]. Although effects on cardiovascular system are less profound, sedative effect induced by medetomidine at 20 μg/kg is less profound than those by a higher dose of medetomidine with more marked individual differences between animals [4]. Attempts have been made to produce preferable sedative condition by combining medetomidine with other drugs [1, 4]. This study demonstrated several advantages of combinations of medetomidine-midazolam and medetomidine-butorphanol in dogs.

The principal advantage of addition of midazolam or butorphanol to medetomidine was an enhancement of sedative effect. These combinations greatly assured the sedative condition, prolonged the duration of lateral recumbency, and depressed the arousal reaction caused by sensory stimuli, which indicated the more longer available duration for clinical procedures than that by medetomi-

dine alone. These combinations invariably produced profound sedative condition, while there were individual differences between animals with medetomidine alone, especially during the induction phase. Even during the maximum sedation induced by a high dose of medetomidine, the dogs often aroused by sound stimuli or painful stimuli. The potent sedative effects induced by medetomidine-butorphanol or medetomidine-midazolam could be considered induced by synergistic interaction of medetomidine and midazolam or butorphanol, because each drug exerts only slight sedative effect when used alone at the dose used in this study and the sedative effects achieved by these combinations were greater than those which could be expected from simple additive effects. Potent sedative effect in the combination of medetomidine and butorphanol has been reported in pigs [16], however the precise mechanism of interaction between α_2-adrenoceptor agonists and opioids is still undetermined [11]. A significant synergism of medetomidine and midazolam in rats has been also reported, indicating that this pharmacodynamic interaction did not include the drugs' receptor binding sites [17]. Although accurate mechanism has been also still unclear, a possible pharmacodynamic mechanism between these two drugs was proposed [5, 17, 22].

Another advantage of use of midazolam or butorphanol with medetomidine was an enhancement of analgesic and muscle relaxant effects. α_2-Adrenoceptor agonists exerts analgesic and muscle relaxant effects through activation of α_2-adrenoceptor, which are characteristic effects of these sedatives. As compared with butorphanol, midazolam enhanced these effects more potently. This combination induced satisfactory sedation for approximately 40 min, even if it is used for various diagnostic procedures that require excellent immobilization such as CT scan and myelography or therapeutic procedures accompanied by light pain. Midazolam has been reported to induce muscle relaxation through making cell membranes more resistant to neuroexcitation by enhancing the chloride channel gating function of GABA [20]. This might be the major reason why midazolam produced profound muscle relaxation and suppressed muscle twitching. It is very interesting that medetomidine-midazolam produced more profound analgesia than medetomidine-butorphanol. The accurate mechanism of this interaction between medetomidine and midazolam is unclear, however these drugs act synergistically because midazolam itself has no analgesic effect in contrast to the relatively potent analgesic effect of butorphanol. Further investigations are needed to clarify the interaction between these two drugs. Furthermore, since addition of midazolam considerably depressed swallowing reflex accompanying with satisfactory muscle relaxation, the combination of medetomidine and midazolam would also allow the oral examinations or minor dental treatments.

The other advantage of using midazolam or butorphanol combined with a low dose of medetomidine is an improvement or reduction of the undesirable effects of medetomidine. Addition of butorphanol prevented vomiting. Vomiting after medetomidine administration is a well-known undesirable effect [7, 24, 28]. In this study, no vomiting was observed in all dogs given medetomidine-butorphanol, while two dogs given 20 μg/kg of medetomidine, two dogs given 40 μg/kg of medetomidine, one dog given 80 μg/kg of medetomidine and three dogs given medetomidine-midazolam (n=7 each) vomited once before the onset of the sedation. It has been reported that the butorphanol effectively reduced vomiting induced by cisplatin, a potent cancer chemotherapy drug, through activation of opiate receptor located in vomiting center [18]. Although the mechanism of the interaction was not clear, an addition of midazolam regularized respiratory pattern and maintained higher respiratory rate. Medetomidine-midazolam also improved inductive and recovery condition lengthening the duration of profound sedation in spite of the reduction of the induction time and total recovery time. In addition, dogs given medetomidine-midazolam showed no twitching as mentioned above, which is one of the frequently noted side effects of medetomidine [4].

The present study demonstrated that combinations of medetomidine (20 μg/kg)-midazolam (0.3 mg/kg) or medetomidine (20 μg/kg)-butorphanol (0.1 mg/kg) exerted potent and preferable sedation even if the dose of medetomidine was reduced. Especially, Me-Mi showed several advantages over any doses of medetomidine alone or Me-B without further side effects. Potent sedative effect induced by Me-Mi was characterized by prompt onset of action, predictable depth and duration, moderate reflex depression and analgesia, excellent muscle relaxation, regular respiration and excellent immobilization. This combination is available and valuable in dogs for most situations that require chemical restraint even if accompanied by light pain.

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