

**CLINICAL COMPARISON OF
MEDETOMIDINE-BUTORPHANOL,
MEDETOMIDINE-MIDAZOLAM AND
MIDAZOLAM-BUTORPHANOL FOR INTRAMUSCULAR
PREMEDICATION IN THE ENGLISH BULLDOG.**

**CONFRONTO DEGLI EFFETTI CLINICI DI
MEDETOMIDINA-BUTORFANOLO,
MEDETOMIDINA-MIDAZOLAM E
MIDAZOLAM-BUTORFANOLO UTILIZZATI PER VIA
INTRAMUSCOLARE NELLA PREMEDICAZIONE DEL
BULLDOG INGLESE**

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Key words

Anaesthesia, sedation, dog, English bulldog.

Parole chiave

Anestesia, sedazione, cane, bulldog inglese.

Summary

The objective of the study is to compare the combinations of medetomidine-butorphanol, midazolam-butorphanol and medetomidine-midazolam for intramuscular premedication in the English bulldog, a brachycephalic breed with an increased anesthesiological risk.

21 English Bulldogs were sedated or anaesthetized. They were divided into three groups (A, B and C) of 7 individuals. The subjects of group A were premedicated with butorphanol (0.2 mg/kg) and medetomidine (7 μ g/kg), the ones of group B with butorphanol (0.2 mg/kg) and midazolam (0.35 mg/kg) and the ones of group C with medetomidine (7 μ g/kg) and midazolam (0.35 mg/kg). Heart and respiratory rates and body temperature were recorded every 5 minutes after premedication. The level of sedation was assessed. General anaesthesia was induced by intravenous administration of propofol and was maintained by isoflurane.

Premedication with midazolam-butorphanol resulted in mild changes, while

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other mixtures caused significant decreases in heart and respiratory rates. Medetomidine-butorphanol produced a better and faster sedation than other combinations. The dose of propofol for induction and the concentration of isoflurane for maintenance were significantly lower when premedicating by medetomidine.

Balanced anaesthesia that combined α_2 -adrenergic agonists, benzodiazepines and opioids is clinically useful and safe in the English bulldog. Medetomidine-butorphanol and medetomidine-midazolam induce a good sedation with appropriate analgesia and muscle relaxation, sufficient for performing procedures of intermediate level of pain. Midazolam-butorphanol produces a poor level of sedation in healthy English Bulldogs, but it may be useful in old and sick subjects because of its minimal cardiorespiratory effects.

Riassunto

Obiettivo dello studio è confrontare gli effetti delle associazioni medetomidina-butorfanolo, midazolam-butorfanolo e medetomidina-midazolam, somministrate per via intramuscolare, nella premedicazione del bulldog inglese, razza brachicefalica con rischi anestesiológicos maggiori.

Abbiamo valutato 21 bulldog inglesi: 2 solo sedati e 19 sedati e poi anestetizzati. Suddivisi in 3 gruppi di 7 soggetti, sono stati premedicati con: gruppo A butorfanolo (0.2 mg/kg) e medetomidina (7 μ g/kg), gruppo B butorfanolo (0.2 mg/kg) e midazolam (0.35 mg/kg), gruppo C medetomidina (7 μ g/kg) e midazolam (0.35 mg/kg). Nei 20 minuti seguenti la premedicazione, sono state rilevate, ogni 5 minuti, frequenze cardiaca e respiratoria, temperatura e valutato il livello di sedazione. L'anestesia è stata indotta con propofol e mantenuta con isofluorano.

L'associazione midazolam-butorfanolo ha avuto minimi effetti depressivi mentre le altre combinazioni hanno determinato una significativa depressione cardiorespiratoria. La sedazione migliore e più rapida è stata ottenuta con medetomidina-butorfanolo. L'utilizzo della medetomidina nella premedicazione ha significativamente ridotto la dose di propofol per l'induzione e la concentrazione d'isofluorano per il mantenimento.

Tutte le associazioni impiegate sono risultate maneggevoli, efficaci e sicure nel bulldog inglese. Medetomidina-butorfanolo e medetomidina-midazolam hanno assicurato una buona sedazione con livelli di analgesia e miorelaxamento sufficienti per procedure mediamente dolorose. L'associazione midazolam-butorfanolo ha determinato uno scarso livello di sedazione, ma per i suoi minimi effetti depressivi cardiopolmonari può essere utilizzata anche in animali anziani e debilitati.

Introduction

The first reference to "bulldog" dates back to 1609. It was originally employed for the "bull baiting" and its features (short legs and muzzle) reflect this. The English bulldog is a brachycephalic breed: its facial index is twice mesocephalic breeds' one. As a consequence, its short skull results in a dog having an excessive amount of nasal and pharyngeal mucosae compressed into a limited bony space, with

poorly developed nares and a soft palate that is too long. These primary anatomical changes produce upper way resistance and obstruction, increased inspiratory effort and excessive negative nasopharyngeal and laryngeal pressures on inspiration. Consequently, these primary changes may cause secondary changes due to the high negative inspiratory pressure: oedema and inflammation of the pharyngeal and laryngeal mucosae, eversion of the laryngeal saccules and, occasionally, laryngeal collapse. The English bulldog sometimes presents also reduction of the cross-sectional of the trachea which further increases the resistance to the air flow and the work of breathing. In addition, vagal tone is frequently high in brachycephalic dogs: vagal stimulation associated with pharyngeal manipulation, caused by difficult intubation, can contribute to significant bradycardia. The most frequently reported clinical signs in patient with brachycephalic syndrome are noisy respirations and/or heat intolerance (4).

Anaesthetic management is related to the severity of clinical signs at presentation and degree of airway obstruction. Some diagnostic and therapeutic procedures are possible only with a good anaesthesia including analgesia and myorelaxation. Balanced anaesthesia that combined α 2-adrenergic agonists, benzodiazepines and opioids is clinically useful. These substances may have also side effects on cardiac and respiratory systems, but it is known that drug combinations with low doses produce more reliable premedication and less side effects than a higher dose of each drug alone (12).

This clinical study was conducted to compare the effects of three different drug combinations, based on medetomidine, midazolam and butorphanol, previously used in other dog's breeds (3, 6, 7, 8, 12, 14), (medetomidine-butorphanol, midazolam-butorphanol and medetomidine-midazolam).

Materials and Methods

The study included 21 English Bulldogs (10 males and 11 females) led to Veterinary Surgery and Emergency Care Section of Animal Health Department of Veterinary Medicine Faculty of Parma.

Their mean age was 25.7 ± 17.3 months (range, 5 to 72 months) and mean body weight 24.4 ± 4.1 kg (range, 15 to 32 kg). Because all patients required sedation or general anesthesia for diagnostic or surgical procedures, they were fasted for 12 hours prior to anaesthetic procedures (table 1). All patients were classified as ASA 2 after a standard clinical examination preceding premedication and general anaesthesia. We asked also to the owners if their dogs showed some clinical signs related to the brachycephalic syndrome.

We used following doses for the premedication: butorphanol (Dolorex, Intervet Italia, Peschiera Borromeo, Italy) 0.2 mg kg⁻¹, medetomidine (Domitor, Pfizer, Rome, Italy) 7 μ g kg⁻¹ and midazolam (Midazolam) 0.35 mg kg⁻¹. English Bulldogs were divided into three groups of 7 individuals (tables 2, 3 and 4) on the basis of drugs combination used for the premedication: group A (medetomidine-butorphanol), group B (midazolam-butorphanol) and group C (medetomidine-midazolam). The mixture was injected intramuscularly in the femoral quadriceps. As soon as pos-

sible we inserted to all animals an intravenous catheter (diameter 22 or 20 G) into cephalic vein and lactated Ringer's solution was infused at the rate of 7-10 ml kg⁻¹ h⁻¹ (Ringer lactate, ACME, Milano, Italy).

The level of sedation was assessed and was classified as good, moderate or poor. Good sedation was such a state when the animal resumed lateral recumbence and it was easy to handle without any defence reaction. Moderate sedation was such a state when the subject took up lateral or sternal recumbence and handling resulted in defence reactions. Poor sedation resulted in the animal not resuming either lateral or sternal recumbence, reacting by defence responses and being able to walk. We recorded the time (minutes after premedication) in which ataxia, sternal recumbence and maximum effect (lateral recumbence and no defence reactions) appeared. We monitored heart and respiratory rates and rectal body temperature prior to premedication (T0) and every five minutes (T5, T10, T15 and T20) for twenty minutes after premedication. Occurrence of adverse reactions was monitored and recorded. If necessary, after preoxygenation with 100% oxygen (O₂) by use a facemask, general anaesthesia was induced with propofol (Rapinovel, Schering-Plough Animal Health, Harefield, UK) in the dose to result in loss of laryngeal reflex that enabled orotracheal intubation performed with a Rüşh probe. Patient were put on a half-closed breathing circuit of the inhalation machine (Fabius, Dragër Italia, Corsico, Italy) and supplied with a mixture of oxygen (flow rate: 100 ml kg⁻¹ min⁻¹) and isoflurane (Isoflurane, Schering-Plough Animal Health, Harefield, Uxbridge, UK). Animals were monitored during general anaesthesia using the monitors PM8050 (Drager Italia, Corsico, Italy) and Guardian Byosis (Schiller, Esaote, Genova, Italy). We administered to the patients submitted to surgical procedures carprofen (Rimadyl) 4 mg kg⁻¹ iv 15 minutes prior to surgery, cefazolin (Cefazolina, Merck, Frankfurter, Germany) 20 mg kg⁻¹ iv at the beginning and at the end of surgery. During recovery, we evaluated the opportunity of the administration of atipamezole (Antisedan, Pfizer, Rome, Italy) in patient sedated using medetomidine.

Results are reported as mean \pm standard deviation (SD). Statistical evaluation was performed using Student t test and included comparison of parameters characterising both groups of animals: age, weight, heart rate, respiratory rate, body temperature, dose of propofol used for the induction of general anesthesia and concentration of isoflurane necessary to maintain a surgical plain of anesthesia. The significance was set at $p < 0.05$.

Results

No significant difference was recorded between groups about weight, while the dogs of group B were significantly younger than animals of group C.

No side effects were recorded in group A. In group B, one dog (dog n° 13) presented apnoea after induction with propofol. In group C, we recorded two cases of apnoea (dogs n° 18 and 19) and two cases of vomiting (dogs n° 16 and 19) after premedication.

5 animals in group A and 6 in group B were administered atipamezole during recovery. The dose (mean \pm SD) administered in groups A and C was respectively

$29.5 \pm 9.7 \mu\text{g kg}^{-1}$ and $22.2 \pm 4.4 \mu\text{g kg}^{-1}$.

Heart rate (table 5)

In groups A and C, heart rates were significantly reduced at T5. These reductions went on at T10, T15 and T20. No significant differences were recorded in group B. Heart rate was significantly higher in group B than in groups A and C at T20.

Respiratory rate (table 6)

In groups A and C, respiratory rates were significantly reduced at T5. These reductions went on at T10, T15 and T20. In group B, all subjects presented polypnea at T5 and T10. The data at T0, T15 and T20 in table 6 regarded only 3 dogs because the others had polypnea.

Body temperature (table 7)

In group A, body temperature increased; this increase was significant at T10 and T15. In group B, body temperature decreased; this reduction was significant at T20. In group C, body temperature was significantly increased at T20.

Level of sedation (table 8)

In groups A and C good level of sedation was achieved in all individuals, but significantly more rapidly in group A than in group C. In group B a moderate level of sedation was achieved in all individuals.

Dose of propofol

Propofol was not used in 2 dogs of group A. The dose of propofol (mean \pm SD) administered to induce general anesthesia in groups A, B and C respectively amounted to $1.6 \pm 0.2 \text{ mg kg}^{-1}$, $2.2 \pm 0.3 \text{ mg kg}^{-1}$ and $1.5 \pm 0.3 \text{ mg kg}^{-1}$. The dose of propofol used to induce general anesthesia was significant lower in groups A and C than in group B. There was no significant difference between groups A and C.

Concentration of isoflurane

The concentration of isoflurane (mean \pm SD) administered to maintain general anesthesia in groups A, B and C respectively amounted to $1.7 \pm 0.2 \%$, $2.2 \pm 0.7 \%$ and $1.8 \pm 0.2 \%$. The concentration of isoflurane to maintain general anesthesia was significant lower in groups A and C than in group B. There was no significant difference between groups A and C.

Discussion

English Bulldogs are usually exuberant and their physical restraint is difficult. Consequently, sedation plays an important role. Premedication has an increased anesthesiological risk because of primary and secondary anatomical changes of the upper way of this breed.

Combination of premedication drugs has been reported to reinforce the sedative and analgesic actions of the single drug with the subsequent reduction in doses and adverse effects (2, 12).

As previously reported (6), also in our study the combination of midazolam and butorphanol produced a moderate level of sedation and mild changes in cardiopulmonary functions because their effects on vital function are minimal (13). Midazolam is used as a tranquilizing in human medicine, but it has not been used alone for small animals because it induced ataxia and transient agitation (2). Consequently,

midazolam is often associated to other drugs in order to avoid these side effects. It is known that midazolam-butorphanol induces mild sedation in healthy and young dogs while produces a deeper sedation in old or sick animals (6). From our point of view, this mixture is not useful for pharmacological restraint of a healthy English Bulldog, but it may be recommended for sick or old subjects or patients with cardiovascular and respiratory disease. The use of medetomidine improves the quality of premedication: a good level of sedation was obtained in all dogs premedicated by a combination containing medetomidine. The maximum effect has been produced more rapidly with medetomidine-butorphanol than medetomidine-midazolam, probably due to better synergism between medetomidine and butorphanol. The synergic mechanism of action of midazolam with medetomidine is unknown while it has been demonstrated that α_2 -adrenergic agonists (medetomidine) and opioids (butorphanol) act synergistically at the central nervous system (CNS) to produce analgesic effect (2) because the distribution of opioids receptors is similar to that of α_2 -adrenoceptors. In fact, sedative effect of the opioids results from a hyperpolarisation of the neurons in the locus coeruleus, where α_2 -adrenoceptors also act (10). The dogs sedated with the mixture medetomidine-butorphanol assumed lateral recumbency within about 8 minutes. Ko et al. (3) reported that medetomidine 30 $\mu\text{g kg}^{-1}$ and butorphanol 0.2 mg kg^{-1} produced lateral recumbency and no defence reactions 6 minutes after the injection. This disagreement is probably attributable to the lower dose of medetomidine we used.

Even if the dose of medetomidine we administered is lower than ones used in other findings (range, 10 to 40 $\mu\text{g kg}^{-1}$), our data agree with results reported in previous works (2, 3, 5, 12). The medetomidine associated with midazolam or butorphanol ensured a good sedation, but produced a decrease of heart and respiratory rates. Medetomidine is a potent selective α_2 -adrenergic agonist with depressive cardiovascular (bradycardia, arrhythmias, rise in vascular resistance and cardiac output drop) and respiratory (bradypnoea) effects (11). We cannot exclude that also butorphanol contributed to the depression of vital function. In fact, butorphanol alone has minimum side effects on cardiovascular system, but the bradycardic effects of medetomidine and butorphanol seemed to be additive (1). The same additive effect has not been demonstrated about medetomidine-midazolam. It is probably that midazolam enhances the sedative effect of medetomidine, but it doesn't very likely play an important role in cardiac and respiratory changes recorded in group C because midazolam itself has minimal cardiopulmonary effects (13). Premedication drugs influence not only cardiorespiratory function, but also body temperature and generally cause hypothermia because of a reduction of basal metabolism. In accordance to this theory, the combination midazolam-butorphanol (group B) produced a decrease of body temperature. On the contrary, in groups A (medetomidine-butorphanol) and C (medetomidine-midazolam) body temperature increased. From our point of view medetomidine played an important role because it has a biphasic mechanism of action: there is a peripheral transient vasoconstrictive effects of α_2 -adrenoceptors, that causes a transient increase of body temperature, followed by a reduction of muscle activity, responsible for the decrease of body temperature (7).

Another side effect recorded during premedication was vomiting. We supposed that it was due to the emetic effect of medetomidine or to the predisposition

of brachycephalic breeds to vomiting during induction and recovery from general anaesthesia (9).

The premedication ensured a sweet induction and produced a sparing effect on the induction dose of propofol and on the concentration of inhalants for the maintenance (8). Likewise in other studies, also in our experience the combination of medetomidine, midazolam and butorphanol as premedicant drugs enabled to use a low induction dose of propofol (6, 14) and a low concentration of isoflurane for the maintenance of general anaesthesia (8). The doses are significantly lower using medetomidine. As reported by Rauser et Lexmaulova (12), it is above all due to the sedative action of medetomidine and its synergic mechanism of action with butorphanol and midazolam. 1 dog in group B and 2 dogs in group C showed temporary apnoea immediately after the administration of propofol. An endotracheal tube was placed and an assisted or controlled ventilation was started with no subsequent complications. From our point of view and in accordance with Paddleford (9), apnoea was probably caused by the excessive speed of administration of propofol.

The recovery must be careful in order to ensure cardiovascular and respiratory functions. Atipamezole may be useful for this purpose. The dose of atipamezole we used was three or four times higher than the preceding medetomidine's one and it has been effective, devoid of side effects and induced a safe recovery (15).

Conclusion

The English bulldog is a brachycephalic breed and has an increased anaesthesiological risk because its primary and secondary anatomical changes cause upper airway obstruction and resistance. Balanced anaesthesia that combined $\alpha 2$ -adrenergic agonists, benzodiazepines and opioids is clinically useful and safe in the English bulldog. Medetomidine-butorphanol and medetomidine-midazolam induce a good sedation with appropriate analgesia and muscle relaxation, sufficient for performing procedures of intermediate level of pain, even if the former combination has a rapid onset of action than the latter. Midazolam-butorphanol produces a poor level of sedation in healthy English Bulldogs, but it may be useful in old and sick subjects because of its minimal cardiorespiratory effects.

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Table 1. Number of diagnostic and surgical procedures in which the patient was in need of sedation (S) or general anesthesia (GA).

Procedure	S	GA
1-Elbows radiograph	1	
2-Epilation of distichiasis	1	
3-Soft palate resection		7
4-Entropion		2
5-Prolapsed third eyelid gland		1
6-Entropion and prolapsed third eyelid gland		1
7-Bilateral elbow arthroscopy		1
8-Trochleoplasty		1
9-Shoulder and elbow radiograph		1
10-Knee arthroscopy		1
11-Endoscopy of the larynx		1
12-Enucleation of the globe		1
13-Laryngeal sacculotomy		1
14-Reconstruction of cruciate ligament		1

Table 2. Patient (indicated with a number), sex (F, female; M, male), procedures (reported with the corresponding number of the table 1), age in months, weight in kg and presence (yes) or absence (no) of brachycephalic syndrome (BS) of subjects of group A (medetomidine-butorphanol). About age and weight, mean \pm standard deviation (SD) is reported.

Patient (Sex)	Procedure	Age (months)	Weight (Kg)	BS
Dog n° 1 (F)	1	15	26	no
Dog n° 2 (F)	8	13	23	no
Dog n° 3 (F)	2	72	25	no
Dog n° 4 (M)	3	12	27	yes
Dog n° 5 (M)	4	22.8	25	no
Dog n° 6 (M)	9	15	26	no
Dog n° 7 (M)	3	24	24	yes
Mean \pm SD		24.8 \pm 21.3	25.1 \pm 1.3	

Table 3. Patient (indicated with a number), sex (F, female; M, male), procedures (reported with the corresponding number of the table 1), age in months, weight in kg and presence (yes) or absence (no) of brachycephalic syndrome (BS) of subjects of group B (midazolam-butorphanol). About age and weight, mean \pm standard deviation (SD) is reported.

Patient (Sex)	Procedure	Age (Months)	Weight (Kg)	BS
Dog n° 8 (M)	3	15	27	yes
Dog n° 9 (F)	4	12	22	no
Dog n° 10 (M)	6	12	26	yes
Dog n° 11 (M)	5	5	21	no
Dog n° 12 (F)	3	5.5	15	yes
Dog n° 13 (F)	10	48	25	no
Dog n° 14 (F)	14	36	20	no
Mean \pm SD		19.1 \pm 16.4	22.3 \pm 4.1	

Table 4. Patient (indicated with a number), sex (F, female; M, male), procedures (reported with the corresponding number of the table 1), age in months, weight in kg and presence (yes) or absence (no) of brachycephalic syndrome (BS) of subjects of group C (medetomidine-midazolam). About age and weight, mean \pm standard deviation (SD) is reported.

Patient (Sex)	Procedure	Age (Months)	Weight (Kg)	BS
Dog n° 15 (M)	12	60	31.6	no
Dog n° 16 (F)	13	36	23	yes
Dog n° 17 (M)	7	15	32	no
Dog n° 18 (M)	3	42	23	yes
Dog n° 19 (F)	3	60	22	yes
Dog n° 20 (M)	3	30	30	yes
Dog n° 21 (F)	11	48	18	yes
Mean \pm SD		41.6 \pm 16.2	25.7 \pm 5.5	

Table 5. Data (mean \pm SD) about heart rate in beats per minute (bpm).

	Group A	Group B	Group C
T0	113.1 \pm 20.9	127.1 \pm 30.5	96.7 \pm 16.3
T5	82.2 \pm 24.6	106.7 \pm 11.5	84.4 \pm 9.3
T10	75.4 \pm 19.9	113.7 \pm 12.5	82.5 \pm 26.1
T15	74.0 \pm 17.9	100.4 \pm 22.5	78.7 \pm 27.3
T20	70.0 \pm 14.7	128.8 \pm 28.9	76.8 \pm 25.5

Table 6. Data (mean \pm SD) about respiratory rate in acts per minute (apm).

	Group A	Group B	Group C
T0	68.3 \pm 57.3	26.7 \pm 8.3	92.4 \pm 38.6
T5	50.0 \pm 44.6	Polypnea	60.8 \pm 25.6
T10	40.8 \pm 30.4	Polypnea	44.8 \pm 20.5
T15	42.7 \pm 37.2	47.2 \pm 37.7	28.7 \pm 16.8
T20	51.2 \pm 34.9	51.2 \pm 34.9	28.0 \pm 10.3

Table 7. Data (mean \pm SD) about rectal body temperature in degrees centigrade ($^{\circ}$ C).

	Group A	Group B	Group C
T0	39.1 \pm 0.3	38.8 \pm 0.3	39.4 \pm 0.8
T5	39.1 \pm 0.3	38.5 \pm 0.3	39.2 \pm 0.3
T10	39.4 \pm 0.7	38.4 \pm 0.3	39.3 \pm 0.4
T15	39.3 \pm 0.6	38.2 \pm 0.4	39.3 \pm 0.5
T20	39.6 \pm 0.8	38.3 \pm 0.5	39.6 \pm 0.9

Table 8. Time of onset in minutes (mean \pm SD) of ataxia, sternal recumbence and lateral recumbence associated with no defence reactions (maximum effect).

	Group A	Group B	Group C
Ataxia	4.3 \pm 0.9	5.0 \pm 4.5	5.0 \pm 1.0
Sternal recumbence	5.7 \pm 3.4	14.6 \pm 4.3	5.4 \pm 1.7
Lateral recumbence and no defence reactions	7.4 \pm 6.4	No subject	11.4 \pm 5.3

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