Clinical Comparison of Medetomidine-butorphanol and Medetomidine-buprenorphine Combinations for Intravenous Premedication of General Anaesthesia in the Dog

P. RAUŠER, L. LEXMAULOVÁ

Department of Surgery and Orthopedics, Small Animal Clinic, Faculty of Veterinary Medicine, University of Veterinary and Pharmaceutical Sciences, Brno, Czech Republic

Received December 12, 2001
Accepted February 13, 2002

Abstract

Raušer P., L. Lexmaulová: *Clinical Comparison of Mmedetomidine-butorphanol and Medetomidine-buprenorphine Combinations for Intravenous Premedication of General Anaesthesia in the Dog.* Acta Vet. Brno 2002, 71: 69-76.

In this study we compared effects of medetomidine (10 μg/kg) with butorphanol (0.1 mg/kg) and medetomidine (10 μg/kg) with buprenorphine (0.01 mg/kg) used for intravenous premedication of general anaesthesia during surgical procedures in clinical practice. The combination of α-adrenergic substances and opioids induced within 5 min good or moderately good sedation. Anaesthesia was induced by intravenous administration of propofol to achieve loss of laryngeal reflex. General anaesthesia was maintained by a mixture of O_2/N_2O/halothane and, at moments of insufficient depth of anaesthesia, it was intensified by propofol re-administration. There was no difference in the dose of propofol for induction of anesthesia between above-mentioned combinations used for premedication. The number of re-administrations and the total dose of propofol re-administered, however, were significantly ($p < 0.05$) lower when premedicating by buprenorphine. We found neither differences in respiratory and heart rates, nor in SpO_2. We found significant ($p < 0.05$) differences in $ETCO_2$ values at the end of anaesthesia, when its concentration was higher in dogs premedicated by the combination of medetomidine-buprenorphine.

α-*adrenergic drugs, opioids, analgesia, sedation, dog*

Painful surgical procedures in a patient are possible only with high-quality anaesthesia including good analgesia and myorelaxation. Premedication plays an important role in this respect, because analgesic and myorelaxant effects of substances used for premedication may have prime importance for the whole anaesthesia. Analgesia is also a parameter, which influences the postoperative period and recovery of the patient from anaesthesia. Analgesia and myorelaxation can be induced by a number of substances of which α_2-adrenergic agonists and opioids belong to commonly used drugs recently.

Medetomidine is a potent selective α_2-adrenergic agonist that has sedative, myorelaxant and analgesic effects (Ko et al. 1996). The level of sedation and analgesia is dependent on the dose administered. Increments of the dose do not result in qualitative changes to the effect, only the duration of anaesthesia changes (Pypendop and Verstegen 1998). Following intravenous administration, medetomidine assumes action within 2 min; analgesia and sedation last approximately 45 and 60-90 min, respectively. Medetomidine has depressive cardiovascular (bradycardia, cardiac output drop, rise in systemic vascular resistance) and respiratory (bradypnoe) effects. Values of blood pressure, however, remain at the same level or are slightly elevated (Pypendop and Verstegen 1998; Pypendop and Verstegen 1999).

Butorphanol is an opioid agonist-antagonist with good analgesic effects (Pfeffer et al. 1980). It induces only mild sedation and has minimum adverse effects to the cardiovascular system. It may cause mild lowering of the heart rate and arterial pressure or slight respiratory depression (Greene et al. 1990; Trim 1983). Its depressive action on respiratory system

Address for correspondence:
MVDr. Petr Raušer
Department of Surgery and Orthopedics, Small Animal Clinic, Faculty of Veterinary Medicine, University of Veterinary and Pharmaceutical Sciences
Palackého 1-3, 612 42 Brno, Czech Republic

Phone: +420 5 4256 2362
Fax + 420 5 4156 2344
E-mail: rauserp@vfu.cz
http://www.vfu.cz/acta-vet/actavet.htm

is, nevertheless, considerably lower than in morphine (Trim 1983; Hosgood 1990). The onset of butorphanol effects after intravenous administration is noted within minutes (e.g., after i.v. administration of 0.4 mg/kg it acts within 3 min). Its effects should last for 2 to 4 h (Hosgood 1990).

Buprenorphine is a partial opioid agonist of a similar character as butorphanol but with higher analgesic potency. The onset of its action is later (15-30 min) and the analgesic effects last for a longer period (8-10 h). Apart from good analgesic effect, it is also characterised by mild sedative and cardiovascular depressive actions (Cowan et al. 1977; Martinez et al. 1997).

Medetomidine administered alone induces sedation (Clarke and England 1989; Young et al. 1990). When combined with opioids, much lower doses are needed for the same sedation effect (Bartram et al. 1993; Bartram et al. 1994; Muir III et al. 1999). Young et al. (1990) mention the same level of sedation induced by a combination of medetomidine (10 μg/kg) with butorphanol (0.1 mg/kg) as after the use of medetomidine alone in the dose of 40 μg/kg. Muir III et al. (1999) consider the sedation by medetomidine alone in middle-aged and older dogs as insufficient. The combination of medetomidine and butorphanol results in optimal sedation together with the subsequent reduction in doses of other anaesthetics needed for the induction and maintenance of anaesthesia. Higher levels and duration of analgesia after the use of reduced doses of medetomidine and opioids are mentioned by some other authors (Grimm et al. 2000; Ko et al. 2000; Ko et al. 1996; Muir III et al. 1999), who also emphasise the reduction of adverse effects of medetomidine to the cardiovascular system. The heart rate is, nevertheless, reduced up to 55% (Bartram et al. 1994) together with mild increase in the blood pressure (Ko et al. 1996). Analgesia following the administration of medetomidine-butorphanol combination lasts even for several hs after the procedure (Grimm et al. 1998). The level of sedation makes diagnostic and simple therapeutic procedures possible (Bartram et al. 1994).

This study is aimed at clinical comparison of anaesthesia levels after premedication by combinations of medetomidine with butorphanol (a less potent and shorter acting opioid characterised by quick onset) and medetomidine with buprenorphine (a more potent and longer acting opioid characterised by slow onset). The dose of propofol used for the induction of anaesthesia or its prolongation at times of insufficient level of inhalation anaesthesia maintained by halothane was used as the main parameter for the evaluation of efficacy of the combination of α_2-adrenergic substances with opioids.

Materials and Methods

Study group of animals

In all, 60 dogs (32 males and 28 females) of 29 breeds at the age of 4.6 ± 3.9 years and weighing 31.6 ± 4.92 kg were included in the study. All the patients were clinically healthy. They were divided into two groups of 30 individuals. They were fasted for 24 h prior to the operation; water was supplied *ad libitum*. Standard clinical examination preceeded general anaesthesia. Anaesthesia was induced for the purpose of performing following surgical procedures: 30 orthopaedic operations (20 arthrotomies, 9 osteosynteses, 1 implant removal), 21 soft tissue surgeries (16 tumour and cyst excisions, 2 external ear canal ablations, 1 treatment of injury, 1 ventral hernia, 1 castration), 7 laparotomies (4 operations on the urogenital tract and 3 procedures on the gastrointestinal tract) and 2 neurosurgical operations (of the spine).

Animals were randomly divided into two groups. Group A comprised 14 dog breeds including mongrels (19 males and 11 females, aged 4.11 ± 3.84 years, weighing 27.9 ± 12.36 kg). Animals of group A were subjected to 15 orthopaedic procedures, 10 soft tissue operations and 5 laparotomies. Group B comprised 15 dog breeds at the age of 5.2 ± 3.94 years and weighing 35.6 ± 16.67 kg. There were 14 males and 16 females in the group B. Group B animals were subjected to 15 orthopaedic procedures, 11 soft tissue surgeries, 2 laparotomies and 2 neurosurgical operations. Both groups comprised similar breeds of dogs. Four breeds (Schnauzer, mongrel, Terrier, Great Dane) were represented in each group.

Protocol of the experiment

To all animals we inserted an intravenous catheter into *v. cephalica antebrachii* or *v. saphena lateralis* (depending on the surgical site). This catheter was then used to administer the mixture of medetomidine (Domitor®) with butorphanol (Beforal®) (MED-BUT, group A) or medetomidine with buprenorphine (Temgesic®) (MED-BUP,

group B) in one syringe. We used following doses: medetomidine 10 g/kg (group A and B), butorphanol 0.2 mg/kg (group A) and buprenorphine 0.01 mg/kg (group B).

The mixture was injected and five min later, after the onset of its effect, the level of sedation was assessed. It was classified as good (level 1), moderately good (level 2) or poor (level 3). Good sedation was such a state when the animal resumed lateral recumbence and it was easy to handle without any defence reactions. Moderately good sedation was such a state when the animal took up lateral or sternal recumbence, handling, however, resulted in defence responses. Poor sedation resulted in the animal not resuming either lateral or sternal recumbence, reacting by defence responses and being able to walk (with a various degree of ataxia). Occurrence of adverse reactions of both substances with regard to possible excitations was carefully monitored during the onset of sedation.

After the onset of sedation, animals were intravenously administered propofol (Propofol Abbott®) in the dose necessary to result in loss of laryngeal reflex that enabled endotracheal intubation. Animals were then put on a half-closed breathing circuit of the inhalation machine Anemat N8 (Chirana) and supplied with a mixture of oxygen, nitrous oxide and halothane (Narcotan®). The concentration of halothane in the breathing system was maintained at 1.5% during the anaesthesia. The animals that were wakening due to insufficient depth of anaesthesia (movements, rise in heart and respiratory rates) were re-administered propofol, even repeatedly if needed, in the dose necessary to the loss of responses. The number of re-administrations and the total dose of propofol were recorded.

Animals were monitored during the anaesthesia using the Cardiocap II (Datex-Ohmeda) machine. Every 10 min following the administration of sedatives (MED-BUT, MED-BUP) we recorded heart and respiratory rates (HR, RR), tissue saturation by oxygen (SpO_2) and the level of CO_2 in expired gasses ($ETCO_2$). Individual parameters were recorded for 70 min, i.e., the duration of medetomidine action (Pypendop and Verstegen 1998; Pypendop and Verstegen 1999).

Statistical evaluation included comparison of parameters characterising both groups of animals (age and weight) as well as parameters measured during the anaesthesia (HR, RR, SpO_2 and $ETCO_2$). Comparison also included the level of sedation and doses of propofol used for the induction of anaesthesia and during re-administrations. We also compared both groups with regard to the number of individual re-administrations of propofol. Regarding frequent disagreement of data with normal distribution, non-parametric methods were used for the statistical evaluation. As there were no paired data in the samples compared, we used the Mann-Whitney test.

Results

Level of sedation

In both groups good and moderately good levels of sedation were achieved in 84% (25 individuals in group A, 25 cases in the group B) and 16% (5 individuals in group A, 5 cases in group B) of patients, respectively. There was no case of poor sedation in any group recorded. The level of sedation was the same in both groups of patients without statistical differences (Table 1).

Dose of propofol

All animals in group A animals were administered propofol in order to achieve the loss of laryngeal reflex. As far as animals in the group B are concerned, propofol was not used in two dogs of this group to induce anaesthesia. The average dose of propofol administered

Table 1
Level of sedation, propofol dose for induction, number of re-administrations and the total dose of propofol as parameters for the evaluation of combinations of medetomidine-butorphanol (group A) and medetomidine-buprenorphine (group B) used for the premedication of general anaesthesia in dogs.

Parameters evaluated	Group A	Group B
Level of sedation (levels 1, 2, 3)	1.1 ± 0.37	1.1 ± 0.38
Propofol dose for induction (mg/kg)	1.4 ± 0.52	1.1 ± 0.51
Number of readministrations	1.1 ± 1.30	0.43 ± 0.73
Total dose of propofol readministered (mg/kg)	1.1 ± 1.68	0.3 ± 0.52

to induce anaesthesia in both groups A and B amounted to 1.3 ± 0.52 mg/kg and 1.1 ± 0.51 mg/kg (Table 1), respectively. There was no significant difference in the dose of propofol administered to induce anaesthesia between group A and B. The mean number of re-administrations during the 70-minute anaesthesia amounted to 1.1 ± 1.31 and 0.4 ± 0.72 (Table 1) in groups A and B, respectively. The total dose of propofol re-administered during the same period amounted to 1.1 ± 1.69 mg/kg and 0.3 ± 0.52 mg/kg (Table 1) in groups A and B, respectively. There were differences in the number of re-administrations and the total dose of propofol re-administered between both groups. Values in group A (MED-BUT) were statistically significantly higher ($p < 0.05$) than in group B (MED-BUP).

Heart and respiratory rates, SpO_2

There were no significant differences between both groups (Fig 1 and 2) in heart or respiratory rates monitored during the 70-min anaesthesia. None of the seven measured time intervals showed significant difference from its counterpart. The value of SpO_2 (Fig 1 and 2) showed no significant differences.

$ETCO_2$

At the beginning of recording, there were no significant differences between group A and B in the concentration of CO_2 in the expired air ($ETCO_2$). At the 50th and 60th min of inhalation anaesthesia, however, the concentration of CO_2 in group B (MED-BUP) was significantly higher ($p < 0.05$) than in group A. Fig. 4 show that at the 70th minute of anaesthesia the difference was even highly significant ($p < 0.01$).

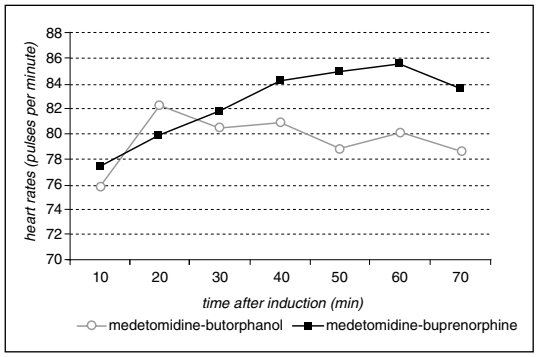

Fig. 1. Changes in heart rates (HR) in combinations of medetomidine 10 µg/kg + butorphanol 0.1 mg/kg and medetomidine 10 µg/kg + buprenorphine 0.01 mg/kg used for the premedication of general anaesthesia in dogs.

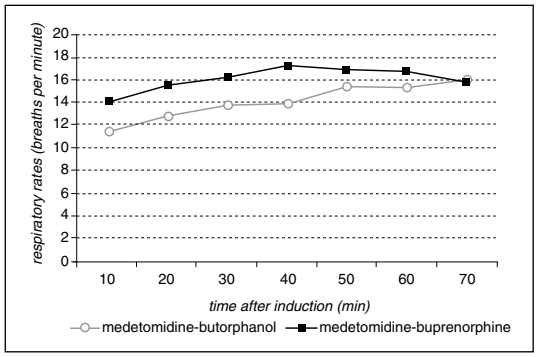

Fig. 2. Changes in respiratory rates (RR) in combinations of medetomidine 10 µg/kg + butorphanol 0.1 mg/kg and medetomidine 10 µg/kg + buprenorphine 0.01 mg/kg used for the premedication of general anaesthesia in dogs.

Discussion

The level of sedation achieved by the administration of medetomidine with butorphanol or medetomidine with buprenorphine was very good in our patients as in those of Bartram et al. (1994) or Muir III et al. (1999). In both groups of patients 84% took up lateral recumbence and allowed handling without any defence responses. We observed no adverse reactions during the onset of sedation. Good or moderately good sedation effects started in most animals up to the time of its evaluation, i.e., within 5 min. Sedative effects of medetomidine after intravenous administration are noted within 2 min (England and Clarke 1989). Effects of butorphanol start also within several min (Hosgood 1990).

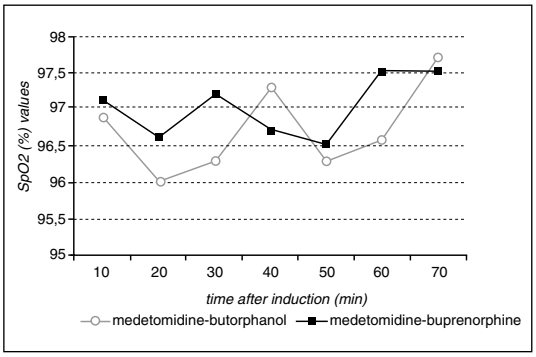

Fig. 3. Changes of SpO_2 values in combinations of medetomidine 10 μg/kg + butorphanol 0.1 mg/kg and medetomidine 10 μg/kg + buprenorphine 0.01 mg/kg used for the premedication of general anaesthesia in dogs.

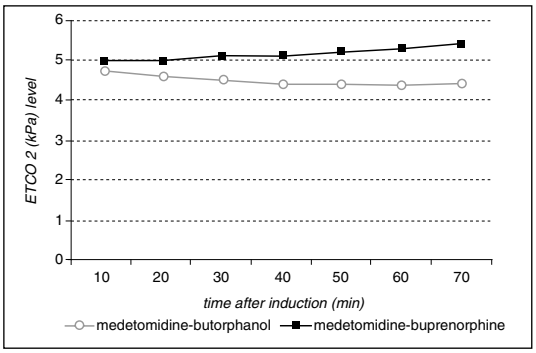

Fig. 4. Changes of $ETCO_2$ values in combinations of medetomidine 10 μg/kg + butorphanol 0.1 mg/kg and medetomidine 10 μg/kg + buprenorphine 0.01 mg/kg used for the premedication of general anaesthesia of dogs.

Effects of buprenorphine, however, are noted much later, i.e., after 15 to 30 min (Covan et al. 1977) which do not fall to our time interval of sedation evaluation. It can, thus, be stated that the main criterion for the onset of sedation evaluated after 5 min of intravenous administration of both substances is the dose and way of medetomidine administration. Animals obtaining the combination of medetomidine with butorphanol were after five min under the influence of both substances, while those obtaining medetomidine with buprenorphine showed only effects of medetomidine. Medetomidine causes sedation of high quality (Ko et al. 1996). Sedation after the use of butorphanol or buprenorphine is considered variable (Hosgood 1990; Covan et al. 1977). As far as the post-op period is concerned, buprenorphine induces analgesia of the same quality as morphine, however, without the outlasting sedation (Brodbelt et al. 1997). Effects of buprenorphine last longer than with butorphanol (Cowan et al. 1977).

The combination of medetomidin-butorphanol has good analgesic, sedative and muscle relaxing effects. This combination induces deep sedation, sufficient for performing procedures of intermediate level of pain, such as radiography of the hip and stifle joint instability (Nečas and Toombs 1999; Toombs and Nečas 1999; Zatloukal et al. 2000). Sufficient analgesia and muscle relaxation is essential for such examinations because it enables measurement of the passive joint laxity. The combination of α-adrenergic substances with opioids for the induction of general anaesthesia is suitable in neurosurgical patients, in particular, in which good sedative and analgesic effects can be employed, for example, for puncturing the subarachnoidal space as a part of diagnosing intervertebral disc disease in dogs (Nečas and Sedláková 1999).

There was no difference in the dose of propofol administered for the induction of anaesthesia (necessary for the laryngeal reflex loss) between the groups. The fact is attributable to the equal sedative action of medetomidine with minimum influence of the opioids. The number of re-administrations of propofol as well as the total dose re-administered during the 70-min evaluation differed between the groups with statistical significance ($p < 0.05$). In group A propofol was re-administered more frequently and in a considerably higher dose. It may be related to analgesic action of both substances because in butorphanol it is lower than in buprenorphine (Pypendop et al. 1996a). For very painful surgical procedures it is better to use more potent buprenorphine, which induces better

analgesia and thus lowers the need of propofol re-administration. It is also in relation with the time of buprenorphine action onset, because surgical procedures usually did not start earlier than 15 min after the administration, i.e. after the onset of its effects (Cowan et al. 1977). Butorphanol (Hosgood 1990) should also be in action at the start of the operation so it is possible to compare the effect of both substances administered together with medetomidine.

There were no significant differences between individual groups in the heart or respiratory rate. No statistically significant differences were found in values of SpO_2. Medetomidine administered in the dose of 40 μg/kg caused cardiovascular depression characterised by bradycardia, in particular. The combination of α-adrenergic substances with opioids can be recommended for the premedication of general inhalation anaesthesia in dogs that are otherwise healthy such as many orthopedic patients. In this case it is possible to employ benefits of these substances without increasing the risk of anaesthesia by their cardiodepressive effects. In small animal practice patients suffering from diseases of the locomotor apparatus are rather numerous (Dvořák et al. 2000; Nečas 1999; Nečas et al. 1999; Nečas et al. 2000), so the number of patients premedicated by α-adrenergic substances in combination with opioids is relatively high. There is no doubt that the reduction of medetomidine dose to 10 μg/kg results in decreasing of adverse cardiodepressive effects even though they may persist. This is evidenced by some heart rate reduction by the above-mentioned lower dose (Bartram et al. 1994). In the framework of our study we noticed some drop in the heart rate in larger dog breeds, in particular. We did not, however, compare the pre-anaesthetic heart rates and those ones during the anaesthesia.

The level of $ETCO_2$ mirrors $PaCO_2$ in the blood, which reflects lung exchange of CO_2 based on sufficient lung ventilation and blood perfusion (Haskins 1996). Changes of $ETCO_2$ are thus reflecting lung ventilation together with cardiovascular apparatus function. Pypendop et al. (1996) compared combinations of medetomidine-midazolam-butorphanol and medetomidine-midazolam-buprenorphine. They mention cardiorespiratory depressive actions of both combinations used, which are characterised by heart rate drop and $PaCO_2$ elevations. They found considerably more profound action of buprenorphine. It is also evident from our results on medetomidine and buprenorphine that the level of $ETCO_2$ (reflecting in relation to ventilation, which was stable, the level of $PaCO_2$) was significantly higher at the 50^{th} and 60^{th} min of anaesthesia and at the 70^{th} min it was even higher with high significance. It may correspond with a more profound action of buprenorphine to the cardiovascular system mentioned by Pypendop et al. (1996). This action, however, is not clinically important in healthy dogs (Martinez et al. 1997). Significant differences in $ETCO_2$ observed only at the 50^{th}, 60^{th} and 70^{th} min might evidence later onset of buprenorphine with a 15-30 min delay as compared to butorphanol. There were, however, no significant differences in the $ETCO_2$ values measured in individual groups at the 30^{th} and 40^{th} min (Fig. 4).

The intravenous administration of medetomidine with butorphanol and buprenorphine, respectively, for the purpose of general anaesthesia premedication induces high-quality sedation with quick onset and considerably reduces the dose of anaesthetics administered during the surgical procedure. It is especially evident when using buprenorphine, which, however, results in the rise of $ETCO_2$ during the anaesthesia.

Klinické srovnání kombinací medetomidin-butorphanol a medetomidin-buprenorphin pro intravenózní premedikaci celkové anestezie psů

V klinické praxi byly srovnány účinky kombinací medetomidinu (10 μg/kg) s butorphanolem (0,1 mg/kg) a medetomidinu (10 μg/kg) s buprenorphinem (0,01 mg/kg) použitých k intravenózní premedikaci celkové inhalační anestezie pro chirurgické zákroky.

Kombinace α-adrenergních látek s opioidy navozovala do 5 min dobrou nebo středně dobrou sedaci. Úvod do anestezie pak byl proveden intravenózní aplikací propofolu do vymizení laryngeálního reflexu. Celková anestezie byla vedena směsí O_2/N_2O/halotan a při nedostatečné hloubce anestezie byla opět prohloubena reaplikací propofolu. Dávka propofolu pro úvod do anestezie se při použití uvedených kombinací látek pro premedikaci výrazně nelišila. Počet reaplikací a celková dávka reaplikovaného propofolu však byla statisticky významně nižší při premedikaci buprenorphinem. Hodnoty dechové a srdeční frekvence, stejně jako SpO_2 se u sledovaných premedikací nelišily. Významné odchylky byly zaznamenány v hodnotách $ETCO_2$ na konci anestezie, jehož koncentrace byla vyšší u psů premedikovaných kombinací medetomidin-buprenorphin.

Acknowledgements

This work was supported by the Ministry of Education, Youth and Sports of the Czech Republic (Research Project No. 161700002).

References

BARTRAM, D. H., DIAMOND, M. J., TUTE, A. S., TRAFFORD, A. W., JONES, R. S. 1994: Use of medetomidine and butorphanol for sedation in dogs. J. Small Anim. Pract. **35**: 495-498

BARTRAM, D. H., YOUNG, L. E., DIAMOND, M. J., GREGG, A. S. JONES, R. S. 1993: Effects of combinations of medetomidine/pethidine when used for sedation and pre-anaesthetic medication in dogs. J. Small Anim. Pract. **34**: 554-558

BRODBELT, D. C., TAYLOR, P. M., STANWAY, G. W. 1997: A comparison of preoperative morphine and buprenorphine for postoperative analgesia for atrhrotomy in dogs. J. Vet. Pharmacol. Ther. **4**: 284-289

CLARKE, K. W., ENGLAND, G. C. W. 1989: Medetomidine, a new sedative-analgesic for use in the dog and its reversal with atipamezole. J. Small Anim. Pract. **30**: 343-348

COWAN, A., DOXEY, J. C., HARRY, E. J. 1977: The animal pharmacology of buprenorphine, an oripavine analgesic agent. Brit. J. Pharmacol. **60**: 547-554

DVOŘÁK, M., NEČAS, A., ZATLOUKAL, J. 2000: Complications of long bone fracture healing in dogs: functional and radiological criteria for their assessment. Acta Vet. Brno **69**: 107-114

ENGLAND, G. C. W., CLARKE, K. W. 1989: The effects of route of administrations upon the efficacy of medetomidine. J. Assoc. Vet. Anaest. **16**: 32-34

GREENE, S. A., HARTSFIELD, S. M., TYNER, C. L. 1990: Cardiovascular effects of butorphanol in halotane anesthetised dogs. Am. J. Vet. Res. **8**: 1276-1279

GRIMM, K. A., THURMON, J. C., OLSON, W. A., TRANQUILLI, W. J., BENSON, G. J. 1998: The pharmacodynamics of thiopental, medetomidine, butorphanol and atropine in beagle dogs. J. Vet. Pharmacol. Ther. **21**: 133-137

GRIMM, K. A., TRANQUILLI, W. J., THURMON, J. C., BENSON, G. J. 2000: Duration of nonresponsive to noxious stimulation after intramuscular admionistration of butorphanol, medetomidine, or a butorphanol-medetomidine combination during isoflurane administration in dogs. Am. J. Vet. Res. **1**: 42-47

HASKINS, S. C. 1996: Monitoring the anaesthetised patient. In: THMON, J. C., TRANQUILLI, W. J., BENSON, G. J.: Lumb & Jones Veterinary Anesthesia. Williams & Wilkins, Baltimore, 3rd ed., pp. 409-423

HOSGOOD, G. 1990: Pharmacologic features of butorphanol in dogs and cats. J. Am. Vet. Med. Assoc. **1**: 135-136

KO, J. C. H., BAILEY, J. E., PABLO, L. S., HEATON-JONES, T. G. 1996: Comparison of sedative and cardiorespiratory effects of medetomidine and medetomidine-butorphanol combination in dogs. Am. J. Vet. Res. **4**: 535-540

KO, J. C. H., FOX, S. M., MANDSAGER, R. E. 2000: Sedative and cardiorespiratory effects of medetomidine, medetomidine-butorphanol, and medetomidine-ketamine in dogs. J. Am. Vet. Med. Assoc. **10**: 1578-1583

MARTINEZ, E. A., HARTSFIELD, S. M., MELENDEZ, L. D., MATTHEWS, N. S., SLATER, M. R. 1997: Cardiovascular effects of buprenorphine in anaesthetised dogs. Am. J. Vet. Res. **11** :1280-1284

MUIR III, W. W., FORD, J. L., KARPA, G. E., HARRISON, E. E., GADAWSKI, J. E. 1999: Effects of intramuscular administration of low doses of medetomidine and medetomidine-butorphanol in middle aged and old dogs. J. Am. Vet. Med. Assoc. **8**: 1116-1120

NEČAS, A. 1999: Clinical aspects of surgical treatment of thoracolumbar disc disease in dogs. A retrospective study of 300 cases. Acta Vet. Brno **68**: 121-130

NEČAS, A., DVOŘÁK, M., ZATLOUKAL, J. 1999: Incidence of osteochondrosis in dogs and its late diagnosis. Acta Vet. Brno **68**: 131-139

NEČAS, A., SEDLÁKOVÁ, D. 1999: Changes in the creatine kinase and lactate dehydrogenase activities in cerebrospinal fluid of dogs with thoracolumbar disc disease. Acta Vet. Brno **68**: 111-120

NEČAS, A, TOOMBS, J. P. 1999: PennHIP v diagnostice dysplazie kyčelního kloubu. In: NEČAS, A., TOOMBS, J. P.: Dysplazie kyčelního kloubu u psů. Artron s.r.o., Brno, pp. 27-31
NEČAS, A., ZATLOUKAL, J., KECOVÁ, H., DVOŘÁK, M. 2000: Predisposition of dog breeds to rupture of the cranial cruciate ligament. Acta Vet. Brno **69**: 305-310
PFEFFER, M., SMYTH, R. D. PITTMAN, K. A., NARDELLA, P. A. 1980: Pharmacokinetics of subcutaneous and intramuscular butorphanol in dogs. J. Pharm. Sci. **69**: 801-803
PYPENDOP, B. H., VERSTEGEN, J. P. 1998: Hemodynamic Effects of Medetomidine in the Dog: A Dose Titration Study. Vet. Surg. **27**: 612-622
PYPENDOP, B., SERTEYN, D., VERSTEGEN, J. 1996: Comparison of the sedative and analgesic effects of medetomidine combined with fentanyl, buprenorphine or butorphanol in the dog. Annales Med. Vet. **1**:17-22
PYPENDOP, B., SERTEYN, D., VERSTEGEN, J. 1996a: Hemodynamic effects of medetomidine-midazolam-butorphanol and medetomidine-midazolam-buprenorphine combinations and reversibility by atipamezole in dogs. Am. J. Vet. Res. **5**: 724-730
PYPENDOP, B., VERSTEGEN, J. 1999: Cardiorespiratory effects of combination of medetomidine, midazolam, and butorphanol in dogs. Am. J. Vet. Res. **9**: 1148-1154
TOOMBS, J. P., NEČAS, A 1999: Rentgenologické vyšetření psa s dysplazií kyčelního kloubu. In: In: NEČAS, A., TOOMBS, J. P.: Dysplazie kyčelního kloubu u psů. Artron s.r.o., Brno, pp. 17-26
TRIM, C. M. 1983: Cardiopulmonary effects of butorphanol tartrate in dogs. Am. J. Vet. Res. **44**: 329-331
YOUNG, L. E., BREARLEY, J. C., RICHARDS, D. L. S., BARTRAM, D. H., JONES, R. S. 1990: Medetomidine as a premedicant in dogs and its reversal by atipamezole. J. Small Anim. Pract. **31**: 554-559
ZATLOUKAL, J., NEČAS, A., DVOŘÁK, M. 2000: Measuring craniocaudal instability in stifle joints of dogs using stress radiographs. Acta Vet. Brno **69**: 311-317