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Comparison of the Antinociceptive Potentiating Effect of Two Opioids when Combined with Detomidine or Diazepam in Dogs

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ABSTRACT

The continuous search for suitable and effective drug combination for dog sedation and analgesia is an aim for most of researchers. The current experimental study aimed to evaluate and compare the sedative, analgesic and cardiorespiratory effects of detomidine/butorphanol, detomidine/nalbuphine, diazepam/butorphanol and diazepam/nalbuphine combinations in sex healthy mongrel dogs. Detomidine-butorphanol or nalbuphine resulted in deep degree of sedation and a reliable period of intense antinociceptive effect. The Longest period of sedation was recorded post diazepam-butorphanol injection. However, diazepam-nalbuphine resulted in the shortest period of both sedation and antinociception. Significant reduction of pulse and respiratory rates was observed post detomidine-opioids combination while diazepam-opioids combination resulted in minimal cardiorespiratory effect. It could be concluded that detomidine-butorphanol induced a strong preemptive antinociceptive effect and a state of balanced anesthesia with minimal response to noxious stimulation.

1. INTRODUCTION

Balanced anesthesia (BA) can be induced using multimodal drug combinations such as tranquilizers, sedatives, and antisialagogue that will act synergistically to relief anxiety and produce sedation (Silver 1959; Lundy, 1962). The high beneficial effect of the BA attracts a lot of researchers to test different drug combinations to maximize its benefits. Opioids is considered one of the drug choice to maximize the output value of the BA, as it minimizes the preoperative pain and anxiety, reduces somatic and autonomic responses to airway manipulations, and provides immediate postoperative analgesia (Fukuda, 2005). Induction of BA by using of benzodiazepines, α2 agonists and opioids was reported by (Verstegen and Petcho, 1993) and (Hayashi et al., 1994). The most common and available analgesics nowadays are nalbuphine and butorphanol which classified as agonist-antagonist opioids similar to morphine and are likely to produce sedation and analgesia (Jaff and Martin, 1985; Pascoe, 2000). Butorphanol was evaluated for its potentiating anesthetic effect in combination with sedatives (Salla et al., 2014; Kellihan et al., 2015, Puighibet et al., 2015; Lee et al., 2016, Tamura et al., 2016) and tranquilizers (Seo et al., 2015). Nalbuphine has been suggested as a good component to provide balanced anesthesia (Crul et al., 1990; Kothari and Sharma, 2013). Regarding its effect on cardiovascular, respiratory, or gastrointestinal effects, nalbuphine proved to have no adverse effect (Sawyer, 1982; Schmidt et al., 1985; Lester et al., 2003). Since butorphanol and nalbuphine are common analgesic for clinical use, a lot of investigations were conducted to compare their effect when injected alone (Murphy and Hug, 1982; Muldoon et al., 1983; Pallasch and Gill, 1985; Vieira et al., 1993, Gringauz et al., 2001, Dabrowska-Wojciak and Piotrowski, 2008) and very little investigation comparing their potentiating effect when combined with other analgesics (Kuzmin et al. 2000, Haw et al. 2016) and according to the author knowledge none of them comparing their combination with detomidine or diazepam.

Diazepam is a benzodiazepines which is used in veterinary medicine for management of separation anxiety, and it also has an anticonvulsant, muscle relaxant and sedative effects (Polzin and Osborne, 1985; Overall, 1997; Schwartz, 2003). It is not only suggested to augment sedation and decrease dose

rate, but also it has been reported to induce minimal cardiovascular and respiratory effects and has a wide range of safety (Clarke and Trim, 2014). Detomidine which is one of α2 agonists was among the drug combinations that have been tested for BA. Detomidine reported to have a higher potent sedative effect than xylazine (England and Clarke, 1996).

The purpose of the present study was to evaluate the sedative, analgesic and cardiorespiratory effects of butorphanol or nalbuphine in combination with detomidine or diazepam for balanced anesthesia in dogs. To the author knowledge, using detomidine in dogs in combination with opioids is unique to this study.

2. MATERIALS and METHODS

2.1. Animals

This study was carried out on six adult healthy mongrel dogs aged between 3 and 5 years old (4 ± 0.79 years) and weighing 17-25 kg (20.8 ± 3.19 kg). All dogs were kept under observation for about one week before the experiment. All study procedures were approved by the Animal Care Committee of the faculty of veterinary medicine, Alexandria University.

2.2. Experiment protocol

The animals were randomly assigned to receive four treatments on different occasions with one-week interval.

1st treatment, dogs were injected with detomidine Hcl (DTM, 0.05mg kg^{-1}, Domosedan, Farmos-Orion Co., Finland) followed by butorphanol (BTR, 0.2mg kg^{-1}, Torbogesic, Fort Dodge Laboratories, Inc., Fort Dodge, Lowa, 50501).

2nd treatment, dogs were injected with detomidine (0.05 mg kg^{-1}) followed by nalbuphine (NLF, 0.5mg kg^{-1}, Alambuphine, Amriya Parm., ind., Egypt).

3rd treatment, dogs were injected with diazepam (DZP, 0.2 mg kg^{-1}, Neuril, Memphis Co. for Pharm.& Chemical Ind.,Cairo, Egypt) followed by butorphanol (0.2 mg kg^{-1}).

4th treatment, dogs were injected with diazepam (0.2mg kg^{-1}) followed by nalbuphine (0.5mg kg^{-1}).

All drugs were given intramuscularly. Food but not water was withheld for 12 hours before the anesthetic procedure.

2.3. Evaluation parameters

The physiological parameters, heart and respiratory rates were measured before drug injection (T_0) then at 5, 10, 15, 30 and 60 minutes post injection. Time to onset and the duration of sedation, antinociception and ataxia were recorded as well as its degree at each time point by the same observer.

Sedation degree was assessed according to (Monteiro et al., 2009) the anesthetized animal was given a score from 1 to 3 according to the following signs; 1, mild sedation (less alert but still active); 2, moderate sedation (drowsy and recumbent but can walk); and 3, Intense sedation (very drowsy and unable to walk). In case the dog evaluated as 3rd score sedation, additional disturbance stimuli (like raising the dogs in walking position and increase the noisy sound) were induced for further investigation.

Antinociceptive effect was evaluated using a pin-prick test. The response to superficial and deep needle pricks at neck, chest, abdomen, fore and hind limb were reported. Tail clamping technique was also used for further antinociceptive effect evaluation using artery forceps. Depth of the antinociception was graded on a score system from 0 to 3; 0, no antinociceptive effect (strong response to noxious stimulus, such as kicking); 1, mild antinociceptive effect (moderate response, such as turning the head towards the site of stimulation); 2, moderate antinociceptive effect (very weak and occasional response); and 3, complete antinociceptive effect (no response to noxious stimulus).

2.4. Statistical analysis

The data were analyzed by descriptive statistical analysis by ANOVA test which was carried out using the SAS system (SAS Institute Inc.). Data were expressed as a mean ± standard deviation. Differences were considered statistically significant if the P-value < 0.05.

3. RESULTS

DTM-BTR was the fastest drug combination in terms of sedation onset (1± 0.01 min) in comparison with the other drug combinations DTM-NLF, DZP-BTR and DZP-NLF in which the sedation onset was at (4.5± 0.50 min), (5± 0.20 min) and (6.5± 1.55 min) respectively (Fig. 1).

The degree of sedation resulted from DTM-BTR injection was scored as deep sedation (score, 3) and at this stage the animals didn't respond to any of the additional induced disturbance stimuli. This stage continued for an average period of 64 min followed by moderate sedation (score 2) which persisted for an average period of 9 min. The total period of sedation was 73± 3.75 min. Degree of sedation post DTM-NLF and DZP-BTR combination didn't significantly differ from DTM-BTR combination.

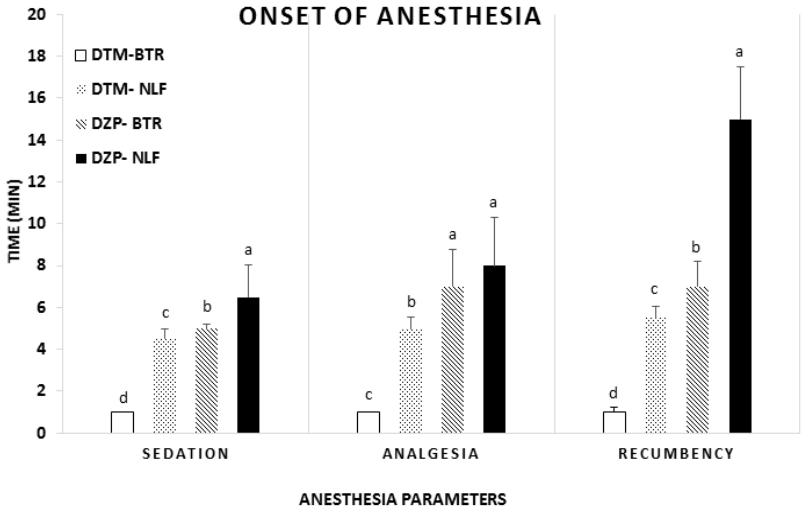

Fig. (1): Onset of sedation, analgesia and recumbency after injection of DTM-BTR, DTM-NLF, DZP-BTR and DZP-NLF in dogs. The data is expressed as the mean ±SD. The different letters denote a significant difference, $p < 0.05$.

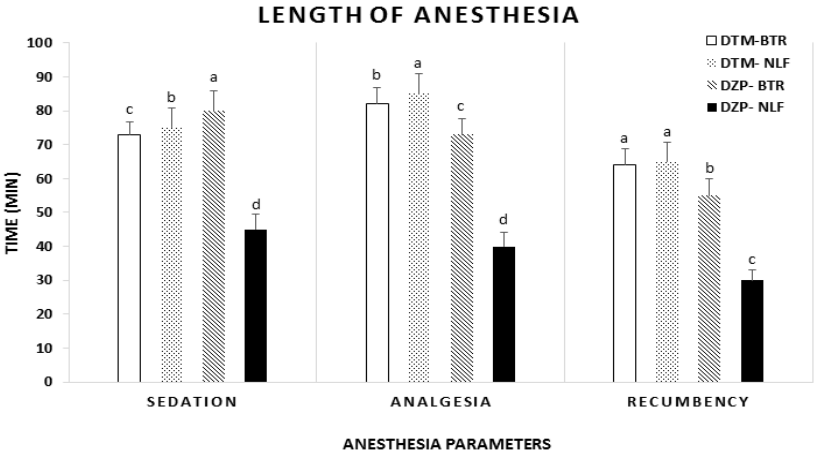

Fig. (2): Assessment of sedation, analgesia and recumbency duration after injection of DTM-BTR, DTM-NLF, DZP-BTR and DZP-NLF in dogs. The data is expressed as the mean ±SD. The different letters denote a significant difference, $p < 0.05$.

The pattern of sedation resulted from DZP-NLF injection was completely different from the other groups, the first 15±0.70 min of the sedation was scored as mild sedation (score 1) characterized by ataxia, agitation, fear and anxiety response to any disturbance, followed by a period of 30 ± 0.56 min of deep sedation in which the animals were easily disturbed with sound stimuli by raising the head for a while but still unable to walk.

The longest duration of sedation was recorded after DZP-BTR (80±5.88 min), followed by DTM-NLF (75±5.77 min) then DTM-BTR (73±3.75 min). The shortest duration was resulted post DZP-NLF combination (45±4.55min) (Fig. 2).

Regarding anti-nociceptive effect evaluation of the different drug combination, the DTM-BTR was again the fastest drug combination to induce antinociceptive effect as it takes only 1±0.01 min to detect its profound and intense effect (score 3) on the dogs and this effect extended for 82±4.88 min. However, the DTM-NLF resulted in deep antinociception similar to DTM-BTR combination; the anti-nociceptive threshold took a little bit longer time evaluated as 5±0.55 min and interestingly, was the longest period of antinociceptive effect compared to the other groups' 85±5.88 min. In the DZP-BTR injected group the antinociceptive effect wasn't intense like the above groups, scored as moderate antinociception (score 2) extended for 73±4.77, the anti-nociceptive threshold was delayed as recorded after 7±1.77 min. While the most delayed anti-nociceptive threshold was recorded after DZP-NLF as 8±2.33 min and its degree was evaluated as moderate antinociception (score 2, which persisted for only 40±4.14 min (Fig. 1, 2).

The ataxia effects recorded after different drug combinations injection come in the same line with the sedation and analgesia onset and duration, as we

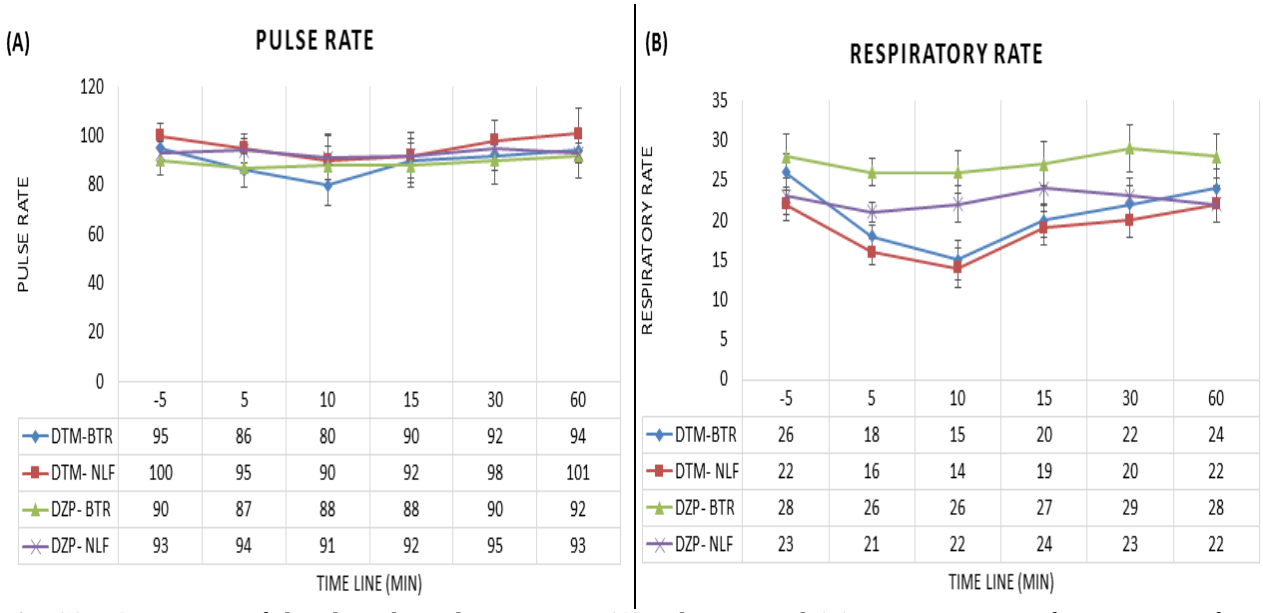

Fig. (3): Assessment of the physiological parameters, (A) pulse rate and (B) respiratory rate after injection of DTM-BTR, DTM-NLF, DZP-BTR and DZP-NLF in dogs at different time points through the experiment.

reported that the fastest recumbency occurred after DTM-BTR combination injection and the most delayed one was noticed after DZP-NLF combination (Fig. 1, 2).

Significant reduction in heart rate and respiratory rate was observed post DTM-BTR and DTM-NLF combination. Minimal effect on pulse and respiratory rates was recorded post injection of DZP-NLF and DZP-BTR combinations. The overall values of respiration and pulse were returned to basal values by the end of the experiment (Fig. 3 A&B).

4. DISCUSSION

Although there is no clear evidence on the adverse effects provoked by DTM injection in dogs, it is not commonly used in pet clinics. The evaluation of BA produced by opioids in combinations with DTM in dogs is unique to this study. In the current study, DTM was used in combination with BTR which resulted in deep and long sedation. The common form of α2 agonist in pet clinics, medetomidine (MDM) showed similar effect when combined with BTR and the author's stated that MDM-BTR could be enough for sedation of dogs to perform various clinical procedures (Bartram et al. 1994). The MDM and its dextro-isomer (dexmedetomidine) (DXM) also has been previously used in similar studies (Bartram et al., 1994, Grimm et al., 2000, Ko et al., 2000, Leppanen et al., 2006, Salla et al., 2014, Puighibet et al., 2015, Lee et al., 2016, Tamura et al., 2016). The same combination in other animal species also proved to be efficient for sedation and antinociception like in equine (Joubert et al., 1999, Abu-Ahmed, 2007) and in ruminant (Carroll et al., 1998, Lin and Riddell, 2003).

However, injection of BTR and NLF each alone have limited analgesic potency (Gunion et al., 2004), it's co-administration with sedatives considered perfect combination as they result in synergistic effect for both sedation and antinociception (Sullivan et al., 1987, Grimm et al., 2000, Lester et al., 2003). This synergism extended to not only potentiated the sedative and analgesic effect but also resulted in longer period than expected. As it have been reported that the half-life of intravenous DTM in dogs is approximately 30 min (Papich, 2015), herein this study we reported extended sedative and analgesic effect more than one hour. It is worth to report that the DTM-NLF combination produced a profound balanced anesthesia for clinical cases introduced to our hospital for castration and wound suturing and didn't required any additional anesthesia techniques (non-published data). Regarding the rapid onset of DTM-BTR was attributed to fast absorption of BTR, as the author findings refer to non-significant difference in the pharmacokinetics of subcutaneous and intramuscular butorphanol injection in dogs (Pfeffer, et al., 1980). Combining NLF with DTM resulted in potent sedative and analgesic effect as well and these finding was similar to those reported after NLF-xylazine combination in dogs (Lester et al., 2003), the same authors stated that the NLF- sedative combination resulted in more potent effect than its combination with acepromazine (tranquilizer), and this confirm the weak and short sedative and analgesic effect of NLF-DZP in the current study. It

is also reported in this group that the animals were easily disturbed to any external stimuli. The same effect reported using benzodiazepines to healthy non-sedated patient (Court and Creenblatt 1992) which may be due to loss of muscle tone and incoordination together with disinhibition of suppressed behavior also benzodiazepines increase fear response and anxiety in excitable animals (Muir et al., 1989).

At combining DZP with BTR the effect was completely different as it resulted in a longer period of deep sedation (80±5.88) and antinociception (73±4.77), this result was in agreement with (Greene, 2002). Although DZP has no analgesic effect (Abou-Madi, 2001) it only produces a reliable sedation especially in older dogs (Lemke, 2007, Rozanski and Rush, 2007, Covey-Crump and Murison, 2008). The longer period of sedation than antinociception in DZP-BTR combination was referred to that DZP is a long-acting potent sedative and muscle relaxant drug, which is owing to its slow metabolism and wide distribution rate in the body (Bateson, 2002, Koshy et al., 2003).

Regarding physiological effects of these combinations on dogs, a significant reduction in heart rate and respiratory rate was recorded in this study at 10 min post injection of both DTM-BTR and DTM-NLF followed by a gradual increase to return to the basal line value by the end of the experiment. Many literatures suggested that BTR has minimal cardiovascular and respiratory effects, but when administered with α2 agonists it increases their depressant effect on heart and respiratory rates (Trim, 1983, Ko, et al., 2000, Sinclair, 2003) also bradycardiac effects of α2 agonists and butorphanol appeared to be additive (Bartram et al. 1994). We proved here in our study that the DTM have the same side effects of MDM and DXM when combined with BTR (Bartram, et al., 1994, Grimm et al., 2000, Ko, et al. 2000, Leppanen et al., 2006, Salla et al., 2014, Puighibet et al., 2015, Lee et al., 2016, Tamura et al., 2016).

The combination of DZP with BTR resulted in minimal cardiorespiratory depression; this result comes in agreement with (Greene, 2002) and (Bryant, 2010). DZP-NLF combination was found to have minimal effect on both respiratory and heart rate and this was supported by (Mazzaferro and Wagner 2001) who stated that benzodiazepines and opioid combination cause a little cardiovascular depression which make it a good choice for patient with high risk of hypertension. NLF also have been shown to have minimal respiratory depression in dogs and other animal species (Flecknell et al., 1991).

5.CONCLUSION

This study demonstrated that the co-administration of DTM and BTR/NLF in dogs appeared to be the most effective combination for balanced anesthesia induction to perform minor surgical operations in healthy dogs in the clinic. However the reduction in both pulse and respiratory rates, they returned to the normal physiological limits by the end of the experiment. DZP-BTR combination produced similar aforementioned sedation and antinociception, with the minimal cardiorespiratory effect but the animals were easily disturbed with external stimuli. The short term of mild sedation and antinociception was recorded post injection of DZP-NLF.

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