The effects of doxapram on haematology, serum biochemical parameters and erythrocyte oxidant/antioxidant status in dogs anaesthetized with propofol

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Abstract
The present prospective randomized experimental study was designed to determine the effects of doxapram on haematological, serum biochemical and antioxidant status in dogs after propofol anaesthesia. Twenty-four healthy male mixed breed dogs, aged 1–2 years, weighing 20.4 ± 2.6 kg was studied. Each dog was anaesthetized twice, with at least one week for washout. Animals were sedated with acepromazine (0.1 mg/kg) intramuscularly. Forty minutes later, anaesthesia was induced using intravenous (IV) propofol (4 mg/kg) titration and maintained for 30 min by propofol (0.2 mg kg⁻¹ min⁻¹). After propofol was discontinued, doxapram (2 mg/kg) hydrochloride was administrated IV in PD treatment while an equal volume of saline was administrated in PS treatment. Blood parameters were analysed in four times: immediately before sedation (T1), after treatment (T2), after complete recovery (T3) and 24 hr later (T4). Haematological assessments revealed no significant difference between treatments except in haematocrit which was significantly reduced at T4 (24 hr later) in PD. A decreasing trend of all haematological variables was observed after doxapram administration until recovery, except monocyte, mean corpuscular haemoglobin, red blood cell distribution width and platelet count. Serum urea, creatinine, glucose, cholesterol, direct bilirubin concentration and alanine aminotransferase activity were not changed following doxapram administration compared to the PS treatment. After doxapram administration, Creatinine (T3), Albumin (T2) and Protein (T2 & T3) decreased while Glucose (T2 & T3) and BT (T3) increased. Antioxidant parameters measured showed no difference between treatments or time. Doxapram (2 mg/kg) IV did not induce any major negative effects on haematological, serum biochemical variables and oxidant/antioxidant status in dogs after propofol anaesthesia.

Keywords
biochemistry, dog, doxapram, haematology, O/A status, propofol
1 | INTRODUCTION

Recovery is an important part of the anaesthetic procedure, when many complications and even death can occur (Brodbelt et al., 2008; Welsh, 2013). Delayed recovery can lead to heart, liver and kidney failure, all of which could be originated from the inadequacy of respiratory system (Tranquilli et al., 2013). Therefore, accelerating the recovery process can reduce the incidence of the mentioned problems due to faster return to physiological conditions (Sabiza et al., 2016, 2018). Doxapram was previously suggested to accelerate recovery from acepromazine (Zapata & Hofmeister, 2013), Thiopental (Evers et al., 1965; Hatch et al., 1985), halothane (Roy & Stullken, 1981), isoflurane (Sabiza et al., 2016), propofol (Sabiza et al., 2018).

Doxapram is a non-selective central nervous system stimulant that works directly at the respiratory centre in the brain stem and also causes carotid and aortic body chemoreceptors stimulation (Wu et al., 2006; Zapata & Hofmeister, 2013). Doxapram is used to stimulate the respiratory system and improve functional activity of larynx in veterinary medicine (Riviere & Papich, 2013). Propofol is an anaesthetic that is widely used for the induction and maintenance of anaesthesia in human and animals (Tranquilli et al., 2013). The authors’ previous study established that doxapram could successfully hasten recovery (about 30 min) from propofol in dogs without unpleasant effects (Sabiza et al., 2018). It was suggested that clinical and cardiorespiratory changes following doxapram administration were the same as saline (control group: Sabiza et al., 2018). However, on the author’s knowledge, there is no study about the effects of doxapram on haematological, biochemical or oxidant/antioxidant status in dogs.

This experimental study was design to determine the effects of doxapram on the mentioned parameters after anaesthesia with propofol in dogs. The authors hypothesized that there would be no clinically significant change in the blood variables following doxapram administration.

2 | MATERIAL AND METHODS

The project was approved by the local Committee of the Institutional Animal Care and Use of Shahid Chamran University of Ahvaz.

2.1 | Animals

This study was carried out on 24 clinically healthy male mixed dogs ranging in age from 1–2 years and weighing 20.4 ± 2.6 kg. The dogs were research animals belonging to the ***. They were housed individually and fed a commercial diet. Dogs were randomly assigned into two treatments: PS group – which received NaCl 0.9% solution, and PD group – which received doxapram hydrochloride. Each dog was studied twice, separated by at least a period of one week. The dogs were numbered and the numbers were selected by withdrawing a lot from a box. Then, the treatment was randomly selected using the same method. Food was withheld for 12 hr and water for 3 hr before the experiment.

2.2 | Procedure

Dogs were sedated with acepromazine at 0.1 mg/kg (Alfasan Co.), administered intramuscularly (IM, Hamstring muscles) (Tranquilli et al., 2013). Then, an angiocatheter (G: 20) was inserted into the left cephalic vein of all dogs. Then, anaesthesia was induced using intravenous (IV) 4 mg/kg propofol titration (Claris Lifesciences Limited; Tranquilli et al., 2013). All dogs were intubated. The animals were allowed to breathe room air. Anaesthesia was then maintained for 30 min by propofol infusion at the rate of 0.2 mg kg^{-1} min^{-1} delivered via the cephalic catheter using an infusion ‘drip’ bag (1 ml = 60 drops) which had been preloaded with propofol and 5% dextrose with concentration of 2 mg/ml (Tranquilli et al., 2013). Thirty minutes after induction, propofol infusion was stopped and immediately after, doxapram at 2 mg/kg (Amdipharm Mercury Company Limited “AMCo”) was administered IV in group PD (Tranquilli et al., 2013). In the PS group, saline was administrated with the same volume as doxapram. Blood sampling was performed four times: immediately before sedation (T1), after saline/doxapram administration (T2), after complete recovery (defined as the dog could walk normally) (T3) and 24 hr later (T4). Physiologic parameters were monitored (PM-9000-2, Burtons, UK) during the anesthetic procedure, including: heart rate (HR), respiratory rate (fR), rectal temperature, noninvasive mean blood pressure, end tidal CO2 (ETCO2) and pulse oximetry (SpO2).

2.3 | Blood sampling and preparation of haemolysate

Blood samples were collected from cephalic veins into anticoagulant (EDTA) containing and plain tubes. The EDTA blood samples were used for haematological assessment and the remaining samples were transformed to haemolysate in order to analyse oxidant/antioxidant status. To prepare haemolysate, erythrocytes were washed 4 times with 0.9% NaCl solution and mixed with cold distilled water. The lysate was subsequently diluted with 0.01 mol/L phosphate buffer pH 7.0, so that a final dilution factor of 100 would be obtained. The prepared haemolysates and serum samples (separated by centrifugation) were then stored at −70°C, until further analysis could be performed.

2.4 | Haematological assessment

Haematological variables including total erythrocyte count (RBC), haematocrit value (HCT), haemoglobin concentration (Hb), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), red blood cell distribution width (RDW), total white blood cells (WBC) and...
platelet count (PLT) were determined by BC-2800Vet haematology analyser (Mindray). Differential leukocyte counts were also estimated manually (Meyer & Harvey, 2004).

2.5 | Determination of oxidant/antioxidant status

The concentration of Malondialdehyde (MDA) in haemolsates was determined as thiobarbituric acid-reactive substances (TBARS), as described by Placer et al. (1966). The quantification of thiobarbituric acid reactive substances (TBARS) was determined by comparing the absorption with the standard curve of MDA equivalents generated by acid catalysed hydrolysis of 1,1,3,3-tetramethoxypropane.

The activity of Superoxide dismutase (SOD) was measured using a commercial kit (Ransod®- Randox Lab, Antrim, UK). Based on the method, superoxide radicals generated by xanthine oxidase reaction convert 1-(4-iodophenyl) -3-(−4-nitrophenol)-5- phenyl tetrazolium chloride quantitatively to a formazan dye. Conversion of superoxide radicals to hydrogen peroxide by superoxide dismutase inhibits dye formation and serves as a measure of superoxide dismutase activity (Ogunro et al., 2013).

Glutathione peroxidase (GPX) enzyme activity was also measured with a commercial kit (Ransel®- Randox Lab). GPX reduces cumene hydroperoxide while oxidizing GSH to GSSG. In the presence of glutathione reductase, GSSG reduced to GSH with concomitant oxidation of NADPH to NADP+. The decrease in NADPH (measured at 340 nm) is proportionate to GPX activity (Agila & Valentine, 1967). GPX activity was then calculated according to the manufacturer’s instructions.

2.6 | Biochemical analysis

Serum biochemical variables including total protein, albumin, glucose, urea, creatinine, cholesterol, total and direct bilirubin concentration, and the activity of alanine aminotransferase (ALT), aspartat aminotransferase (AST) were assessed with a biochemistry autoanalyser (BT-1500, Biotechnica) using colorimetric kit method (Parsazmun).

2.7 | Statistical analysis

IBM SPSS Version 23 (SPSS Inc.) was used for data analysis. An independent sample t-test was used for the analysis of the data between treatments. A repeated measures ANOVA with Bonferroni method were used to analyse the data between the times of the study in each treatment. Results are reported as mean ± standard deviation (SD) with confidence level of 95%.

3 | RESULTS

Mean weight of PS and PD treatments was respectively 20.5 ± 2.8 and 20.4 ± 2.7 with no significant difference. Drug calculations and drug administration were done by one investigator who was unaware of the treatment identity, and all data were recorded by another investigator who was unaware of treatment.

3.1 | Haematological assessment

Results for haematological variables are presented in Table 1. Haematocrit was lower in PD (49.21 ± 2.93) compared with PS (53.86 ± 3.35) on T4 (p = .02). There was a decrease when compared with T0 for RBC at T3 (p = .01) on PS, and at T2 (p = .05) and T3 (p = .02) on PD; Hb at T3 (p = .01) on PS, and at T2 (p = .006) and T3 (p = .02) on PD; HCT at T3 (p = .03) on PS, and at T2 (p = .01), T3 (p = .04) and T4 (p = .03) on PD.

3.2 | Biochemical assessment

Results for biochemical assessments are presented in Table 2. The only significant difference between both groups, were in albumin concentration at T2 (PS > PD, p = .03) and T4 (PS < PD, p = .02), total protein concentration at T3 (PS < PD, p = .01), total bilirubin concentration at T3 (PS < PD, p = .01) and AST activity at T4 (PS > PD, p = .003). Comparison between different sampling times with baseline in PS revealed that glucose concentration (at T2, p = .01; T3, p = .001) increased and protein concentration (at T3, p = .006) and total bilirubin (at T3, p = .01) decreased. In treatment PD, creatinine (at T3, p = .03), albumin (at T2, p = .03) and total protein (at T2, p = .006; T3, p = .02) decreased while glucose (at T2, p = .01; T3, p = .02) and total bilirubitran concentration (at T3, p = .02) increased in comparison to baseline. (Table 2).

3.3 | Lipid peroxidation and antioxidant status

The mean ± SD of SOD and GPX activity and MDA concentration are shown in Table 3. None of the mentioned oxidant/antioxidant markers were significantly different between treatments or between the different time points in each treatment.

4 | DISCUSSION

The only major event following doxapram administration was a noticeable increase in heart rate and blood pressure, while both variables were still within normal range. It can be attributed to doxapram’s stimulating effect on CNS including cardiovascular center in the brain (Yost, 2006; Young & Taylor, 1993). A number of adverse effects have been reported with the use of doxapram, most noticeably, tachycardia, cardiac arrhythmia, hypertension, excitation, anxiety reactions, and even panic attacks (Kim et al., 2013; Wu et al., 2006). Since the author’s previous study revealed that doxapram hastens recovery (Sabiza et al., 2018), recovery time was
not recorded and is not discussed here. In this study, no significant difference was found in haematological assessments between treatments, except in HCT which was significantly declined in PD treatment at T4 (24 hr later).

In a previous study, rapid administration of doxapram resulted in haemolysis, leading to a decrease in haemoglobin and haematocrit, and in leukopenia and may cause further decrease in WBC in pre-existing leukopenia patients (Hochadel, 2015). Despite the reduction in WBC, RBC, Hct and Hb following doxapram administration, the changes were not significant when compared to PS treatment. Hence, doxapram does not seem to have induced the changes observed in the present study.

Biochemical assessments in the present study revealed that the only significant differences between treatments were in albumin, total protein, total bilirubin and AST activity. Both albumin and total protein concentrations increased after a transient reduction immediately following doxapram administration (T2), so that the two analytes were significantly higher in PD compared to PS at the fourth and third sampling time, respectively. Elevation in serum albumin level was reported earlier due to doxapram administration (Hochadel, 2015), which was in agreement with the findings of this experiment. Doxapram is metabolized in the liver. There was an increasing trend in glucose level after anaesthesia in both treatments, but without difference between. Doxapram probably increases the release of catecholamines (Yost, 2006), which may result in an increase in glucose level. Propofol may also have an indirect effect on glucose by suppressing glucose metabolism leading to a hyperglycemic status (Maeda et al., 2018). Therefore, doxapram did not seem to have an impact on glucose level in the current experiment.

A significant rise of lipid peroxide and a major reduction in SOD and GPX activity and α-tocopherol in liver were reported following doxapram administration in mice. It was suggested that an increase of superoxide anion and an inhibition of free radical scavenging reactions might be produced by the drug (Sasaki et al., 1982). However, doxapram did not negatively change O/A status in this study which

| Haematological parameters | Groups | T1 (Baseline) | T2 (b) | T3 (c) | T4 (d) |
|---------------------------|--------|---------------|--------|--------|--------|
| WBC (×10³/µl)             | PS     | 11.10 ± 2.98  | 9.78 ± 2.51 | 9.86 ± 1.74 | 11.10 ± 3.04 |
|                           | PD     | 11.41 ± 1.40  | 9.35 ± 1.08 † | 9.30 ± 1.27 † | 10.96 ± 2.00 |
| Neut (×10³/µl)            | PS     | 9.16 ± 2.78   | 8.15 ± 2.43 | 8.33 ± 2.07 | 8.81 ± 2.86 |
|                           | PD     | 9.38 ± 1.32   | 7.93 ± 1.08 † | 7.70 ± 1.05 † | 8.41 ± 1.71 † |
| Lymph (×10³/µl)           | PS     | 1.60 ± 0.32   | 1.33 ± 0.56 | 1.21 ± 0.56 | 1.83 ± 0.20 † |
|                           | PD     | 1.68 ± 0.23   | 1.11 ± 0.22 † | 1.26 ± 0.57 | 2.11 ± 1.09 |
| Mon (×10³/µl)             | PS     | 0.33 ± 0.05   | 0.30 ± 0.08 | 0.31 ± 0.04 | 0.45 ± 0.15 |
|                           | PD     | 0.35 ± 0.08   | 0.30 ± 0.06 | 0.33 ± 0.05 | 0.43 ± 0.15 |
| RBC (×10⁶/µl)             | PS     | 6.66 ± 0.88   | 5.58 ± 1.30 | 5.35 ± 0.31 † | 6.65 ± 0.49 |
|                           | PD     | 6.32 ± 0.60   | 5.18 ± 0.28 † | 5.49 ± 0.44 † | 6.28 ± 0.32 |
| Hb (g/dl)                 | PS     | 14.73 ± 2.51  | 12.16 ± 2.90 | 11.45 ± 0.87 † | 14.43 ± 0.99 |
|                           | PD     | 13.48 ± 1.14  | 10.95 ± 0.79 † | 11.65 ± 0.78 † | 13.50 ± 0.86 |
| HCT (%)                   | PS     | 49.35 ± 8.59  | 42.41 ± 7.85 | 40.91 ± 2.67 † | 53.86 ± 3.35 |
|                           | PD     | 45.46 ± 2.64  | 38.95 ± 2.63 † | 41.31 ± 3.06 † | 49.21 ± 2.93 † |
| MCV (fl)                  | PS     | 74.01 ± 5.24  | 76.56 ± 3.91 † | 76.61 ± 4.40 † | 81.15 ± 3.45 † |
|                           | PD     | 72.26 ± 3.76  | 75.38 ± 5.25 † | 75.40 ± 4.96 † | 78.55 ± 5.68 † |
| MCH (pg)                  | PS     | 22.01 ± 0.96  | 21.71 ± 0.97 | 21.33 ± 0.93 † | 21.66 ± 0.95 |
|                           | PD     | 21.31 ± 0.77  | 21.08 ± 0.95 | 21.20 ± 1.26 | 21.45 ± 1.44 |
| MCHC (g/dl)               | PS     | 29.81 ± 1.25  | 28.45 ± 1.33 | 27.95 ± 1.06 † | 26.73 ± 0.33 † |
|                           | PD     | 29.56 ± 0.85  | 28.06 ± 1.31 † | 28.16 ± 0.73 † | 27.38 ± 0.72 † |
| RDW (%)                   | PS     | 11.61 ± 0.83  | 12.55 ± 1.48 | 11.20 ± 0.69 | 11.35 ± 0.72 |
|                           | PD     | 12.00 ± 1.42  | 11.53 ± 0.76 | 11.60 ± 0.92 | 11.06 ± 0.42 |
| PLT (×10³/µl)             | PS     | 259.75 ± 30.51 | 269.50 ± 17.25 | 238.75 ± 52.32 | 267.75 ± 21.65 |
|                           | PD     | 259.33 ± 11.67 | 240.75 ± 19.36 | 231.33 ± 9.07 | 270.50 ± 12.55 |

*Significantly different from treatment PS (p < .05)
†Significantly different compared with baseline within a treatment (p < .05).
was in agreement with Kanno and colleagues who reported no significant alteration in plasma lipid peroxides following doxapram administration (Kanno et al., 1998). This finding suggests that doxapram does not exert a relevant influence on the oxidant/antioxidant status in healthy animals. However, further studies in other clinical situations are needed to evaluate the effects of doxapram under different conditions. In the present study, propofol was used as induction and maintenance agent. This drug was previously described as having potential antioxidant effects in dogs (Lee & Kim, 2012; Volti et al., 2006). Propofol might have masked oxidative effects of doxapram in the present study and the counteraction between propofol and doxapram resulted in a balanced O/A status which is comparable to saline.

There were some limitations in the current experiment. This study was performed in healthy dogs; therefore, the results may vary when doxapram is administered in patients with different clinical conditions. Since sedation with acepromazine, a drug known to produce significant haematological effects, could make it more challenging to detect doxapram effects of smaller magnitude, the use of other sedatives is recommended for further investigations. Also, determination of doxapram's sole effect on the above-mentioned parameters are necessary prior to investigation of doxapram effects after anaesthesia.
CONCLUSION

Doxapram (2 mg/kg, IV) did not have any major negative effects on haematological, and serum biochemical parameters and oxidant/antioxidant status in dogs under Propofol anaesthesia. However, CBC analysis, heart rate and blood pressure monitoring are critical prior to doxapram administration.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS’ CONTRIBUTIONS

SS: study design, statistical analysis and preparation of manuscript; HN: Sampling, drug calculation and administration; SMJ: haematology, serum biochemical parameters and erythrocyte oxidant/antioxidant status assessment; AB: study design and preparation of manuscript; BM: study design and preparation of manuscript.

AUTHOR CONTRIBUTION

Soroush Sabiza: Methodology; Project administration; Supervision; Writing-original draft; Writing-review & editing. Hadi Naddaf: Investigation; Methodology; Validation. Seyedeh Missagh Jalali: Conceptualization; Formal analysis; Investigation. Ali Baniadam: Data curation; Visualization. Bahman Mosallanejad: Conceptualization; Data curation; Investigation; Visualization.

PEER REVIEW

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