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Preanaesthetic Medication of Piroxicam with Propofol in Male Dogs Undergoing Gastrotomy

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Abstract

PROPOFOL IS an alcohol used for the induction and maintenance of general anesthesia in dogs. Unfortunately, it is associated with less duration of action, cardiac arrest, and death. Hence the preanaesthetic medication of piroxicam with propofol was studied in Nigerian indigenous dogs undergoing gastrotomy. A randomised control trial was adopted for the study. Ten one-year old male dogs that weighed 5.3 ±0.5 kg divided into two groups of 5 each were used. Propofol (6 mg/kg) was infused three times into cephalic vein of all the ten dogs, whereas one group was further administered 2.2 mg/kg and the other group was administered 4.4 mg/kg of piroxicam, respectively. Duration of onset and maintenance of anaesthesia were significantly lower ($p<0.05$) at 2.2 mg/kg and higher ($p<0.05$) in 4.4 mg/kg of piroxicam group, respectively. Heart rate was significantly higher ($p<0.05$) whereas respiratory rate was significantly lower ($p<0.05$) in both groups. Concentration of piroxicam in both group was significantly higher ($p<0.05$) throughout the study. Hence, piroxicam provided a good, smooth preanaesthetic medication when administered 15 minutes before propofol in dogs during gastrotomy. Preanaesthetic medication of piroxicam with propofol prevented propofol infusion syndrome that caused heart failure, hepatomegaly, fever and sometimes death.

Keywords: Gastrotomy, propofol, piroxicam, general anaesthesia, dog.

Introduction

Vomiting could be due to gastric outflow obstruction caused by foreign bodies, irritation of the mucosa lining of stomach or gastritis [1]. The presence of wooden and metallic foreign bodies has been reported in the intestine and stomach of dogs in Nigeria [2].

Propofol is an ultra-short- acting intravenous anaesthetic agent, used for procedural sedation, and general anesthesia [3]. It is rapidly metabolised in the liver and excreted in the urine. Propofol reduces cerebral metabolism and lowers consistently intracranial pressure [4]. Propofol is prepared in a lipid emulsion, which gives it a characteristic milky white appearance. The formulation contains soyabean oil, glycerol, egg lecithin, and a small amount of the preservative ethylene diamine tetra acetate. A strict aseptic technique must be applied when drawing up propofol, as the emulsion supports microbial growth [3]. The use of propofol for maintenance of balanced general anesthesia is well known to anesthetic practitioners around the world [5]. Propofol has no significant advantages over the popular barbiturates [6-7]. It has antipruritic, anti-anxiolytic and bronchodilatory, muscle relaxation and anti-epileptic properties [4]. Myoclonus, opistotonus, and tonic-clonic convulsions are seen occasionally, when inhibitory centres, have been depressed [8]. The mechanism of action of propofol as an anti-emetic is by inhibition of serotonin release via enhancing gamma amino butyric acid (GABA) activities, in the postrema/chemoreceptor trigger zone [9]. Its use is associated with longer induction

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times and a higher incidence of pain at injection sites [10-11].

Piroxicam, binds with plasma proteins, has a half-life of 50 hours, and is excreted in the urine and feces [12]. It could cause somnolence, lethargy, and flaccid paralysis [13], and offers neuroprotection in cerebral ischemia [14], which may be positively correlated with lipid solubility at high doses [15]. Piroxicam is also known to inhibit potent aquaporin- 4, renders neuroprotection in focal cerebral ischemia in rats, and may be used for the treatment of brain stroke [14]. It is usually available in capsules, tablets, and as a prescription- free gel 0.5% [16]. Piroxicam is one of the NSAIDs that can be given through parenteral routes [17]. The stimulatory, depressant, and analgesic effects of piroxicam [15, 18] could be explored for preanesthetic medication with propofol in dogs undergoing gastrotomy, with the intent of avoiding cardiac arrest and death.

Material and Methods

Animals

A total of 10 male dogs that weighed 5.3±0.5 kg, of about 1-year-old were obtained from dog breeders in Makurdi metropolis. They were housed in the kennels of the Veterinary Teaching Hospital, Federal University of Agriculture, Makurdi. Feed and water were provided *ad libitum*. The animals were acclimatized for several weeks before the commencement of the research drugs.

Propofol (6 mg/kg) and piroxicam (20mg/2mL) were intramuscularly administered into the right and left jugular vein, respectively, for the induction and maintenance of anaesthesia. The doses of piroxicam and propofol were determined according to the method of Saganuwan *et al*. [19] and Watney and Pablo [20]. Each millilitre of emulsion of propofol used contained 10 mg of propofol in a vehicle containing soyabean oil, disodium edetate, purified edetate, purified lecithin, glycerol, and water. It had batch number 621006 with a manufacturing date of 04/2020 and an expiry date of 03/2022, respectively. The drug was manufactured by Neon Laboratories Limited, Mumbai, India. One ampoule of piroxicam (2 ml) contains 20 mg of the ingredient with batch number 181204 manufactured by Shandong Xier Kangtai Pharmaceutical Company Limited, China.

Surgical preparation

The animals were grouped into two groups, each comprising five male dogs. Piroxicam (4.4 mg/kg) was administered to the first group, and 2.2 mg/kg of the drug was administererated to the second group of animals, respectively. Vital parameters such as temperature, pulse rate , respiratory rate, and heart rate were recorded at 0.0, 0.5, 3.0, 6.0, 12.0, and 24.0 h. The dogs were prepared aseptically for surgery using chlorhexidine (0.05%). Blood samples were collected prior to the administration of propofol and piroxicam at 0.0, 0.5, 6.0, 12.0, and 24.0 h of the experimentation.

Gastrotomy

The animals were placed in dorsal recumbency and the surgical site was draped. Piroxicam (4.4 mg/kg) was administered intravenously to five dogs. After 15 minutes of the administration, propofol (6 mg/kg) was administered, intravenously. Another 5 dogs were intravenously administered 2.2 mg/kg of piroxicam, and after the administration, the dogs were infused with propofol (6 mg/kg). However, 3-4 infusions between 10 and 15 minutes intervals yielded perfect general anaesthesia.

A ventral midline abdominal skin incision was made from the xiphoid process to the pubis, through the subcutaneous tissue and linea alba (Fig. 1). A retractor was used to retract the abdominal wall to provide adequate exposure to the abdominal cavity. Inspection of the entire abdominal contents was carried out before incising the stomach wall (Fig. 2).

A gastric incision was made on a hypovascular area of the ventral aspect of the stomach, between the greater and lesser curvatures. The stomach was carefully held to prevent spillage of the gastric contents (Fig. 3), observed, and examined for the presence of any foreign materials (Fig. 4). The incision on the stomach wall was closed with chromic catgut size 2-0, using an inverting Connell suture pattern, which was followed by a simple continuous suture pattern. The abdominal incision was also closed using chromic catgut size 2.0 using a simple continuous suture pattern. The subcutis was closed using a subcuticular suture pattern with a 2.0 inch chromic catgut. The skin incision was then closed with nylon suture material using a horizontal mattress suture pattern (Fig. 5).

Post-operative management

Elizabethan collars were used for each dog, to prevent mutilation of the surgical site. The dogs were kept for two weeks post-surgery and provided with a bland diet and water. Penicillin (22 mg/kg) was administered for a period of two weeks. Sutures were removed after 2 weeks of the surgery.

Assay of piroxicam

The modified method of Akogwu *et* al. [21] was adopted. Blood samples were collected at 0.0, 0.5, 3.0, 6.0, 12.0, and 24.0 h, respectively, and placed in a blood tube without anticoagulant to obtain serum for the piroxicam assay. The serum was refrigerated at 4ºC until ready to use. Each sample was centrifuged for 5 minutes at 3500 rpm to obtain serum. The serum was transferred into a new tube using a micropipette, and 0.5 ml of the serum sample was placed in separate tubes. However, 2.5 ml of acetonitrite was added to each sample and mixed well before centrifuging for 5 minutes at 3,500 rpm.

However, 0.5 ml of supernatant was transferred into a new tube, and 0.1 ml of perchloric acid was added. The samples were placed in the spectrophotometer and read at a wavelength of 380 nm.

Assay of piroxicam standard

Piroxicam capsule (20 mg/kg) was diluted at various concentrations; 10 mg/ml, 20 mg/ml, 30 mg/ml, 40 mg/ml, 50 mg/ml, 60 mg/ml, 70 mg/ml, 80 mg/ml, 90 mg/ml, and 100 mg/ml, respectively. A regression line was drawn to determine the lowest limit of detection (LDD).

Determination of the piroxicam limit of detection

The quantity of piroxicam present in the serum was calculated as follows:

$$Conc.of\ piroxicam\ (\mu g/ml) = \frac{Conc.of\ Standard\ \times Optical\ Density\ of\ piroxicam}{Optical\ Density\ of\ Standard}$$

Statistical analysis

Data generated on quantity of propofol administered, onset of anaesthesia, duration of anaesthesia and duration of surgery were analysed using student-t test paired, and significant difference was determined between the two groups of treatments at 5% level. However, data generated on onset of anaesthesia, duration of anaesthesia, vital parameters, and piroxicam concentration were presented in tabular form. A two- way analysis of variance (ANOVA) was used to analyse the data, and the least significant difference was detected at the 5 percent level [22].

Results

The quantity of propofol used and the onset of anaesthesia were significantly lower ($p<0.05$), whereas the duration of anaesthesia and surgery were significantly higher ($p<0.05$) in dogs administered 6 mg/kg of propofol and 2.2 mg/kg body weight of piroxicam (Table 1). Heart rate and pulse rate were significantly higher ($p<0.05$) at 0.5, 3.0, 6.0, 12.0, and 24.0 h post treatment of propofol. However, the respiratory rate was significantly lower ($p<0.05$) at 12.0 and 24.0 h post treatment of propofol in the group administered 4.4 mg/kg body weight of piroxicam (Table 2). Nevertheless, heart rate was significantly ($p<0.05$) increased at 0.5, 3.0, 6.0, and 12.0 h, whereas respiratory rate was significantly decreased at 0.5, 3.0, 6.0, 12.0, and 24.0 h in the group administered 2.2 mg/kg of piroxicam and 6 mg/kg body weight of propofol, respectively (Table 2). There was no significant difference ($p>0.05$) in concentration between the groups administered 4.4 mg/kg and 2.2 mg/kg of piroxicam. (Table 3).

Discussion

The decreased onset of anaesthesia caused by 2.2 mg/kg of piroxicam observed in the present study in comparison with the dogs treated with 4.4 m g/kg body weight, shows that piroxicam increases the onset of anaesthesia of propofol. However, the increased duration of anaesthesia in the 2.2 mg/kg piroxicam- treated group shows that a lower dose of piroxicam could be combined with 6 mg/kg propofol for balanced anaesthesia in dogs undergoing gastrotomy. The increased duration of surgery observed in the group treated with 2.2 mg/kg of piroxicam may indicate that low onset of anaesthesia may cause low analgesia that may lead to increased sensitivity of the animal to surgical pain. The increased pulse rate and heart rate observed in the group treated with 4.4 mg/kg of piroxicam as compared to the group treated with 2.2 mg/kg of piroxicam, shows that piroxicam may have chronotropic effect in the heart and blood vessels. Hence, piroxicam has effect on the tonicity of respiratory blood vessels, which may not pose threat of triggering attack to asthmatics as other non-steroidal anti-inflammatory drugs do. Piroxicam undergoes keto- enol tautomerism, and so can change to alchohol [18-23], thereby potentiating the anesthetic effect of propofol.

The lack of salivation observed in the two groups of animals could be attributed to piroxicam pretreatment. Propofol caused apnoea and salivation [24]. Improved anaesthesia observed in the group administered piroxicam 2.2 mg/kg in comparison with 4.4 mg/kg may show that piroxicam may have biphasic dose response characterized by therapeutic window phenomenon when pretreated with propofol [25]. The finding agrees with the report indicating that piroxicam depresses central nervous system [24]. Hence, piroxicam has a sedative- analgesic effect [18]. Higher concentrations of piroxicam observed from 0.0- 24.0 h agrees with the report of Akogwu *et al*. [21] indicating that piroxicam lasts longer in the biological system, and propofol lasts longer during intraabdominal surgery [26]. It also undergoes extensive pharmacokinetic and pharmacodynamics interactions with other drugs [27]. End stage renal disease could affect elimination of propofol [28]. Propofol- piroxicam cyclo dextran formulation may be of high clinical value in veterinary surgery. Such formulation could provide anti-inflammatory, and reduced hyperlipidemic-related side effects, obviating the need for formulation of 1% in 10% soyabean oil [29]. Propofol- piroxicam combination may also prevent metabolic acidosis, rhabdomyolysis, hypotension, bradyarrhythmia and myocardial failure that are caused by propofol [30]. High dose infusion of propofol over a long period of time could cause propofol infusion syndrome characterized by fever,

hepatomegaly, heart failure and electrocardiographic changes [31].

The use of polymeric carriers such as propylene glycol, poly (DL-lactide) and poly (lactic-co-glycolic acid) could transport piroxicam efficiently against propofol infusion syndrome [32]. However, the safety of therapeutic agents is dependent on dose of drug, body weight, and body surface area of animal [33]. Combined preanaesthetic medication of piroxicam with propofol could be via brain stem [34] and may be dependent on their functional groups [35]. Therefore, higher dose of piroxicam may damage basal ganglia [36]. Hence piroxicam used at lower doses could reduce puzzling evidence posed by propofol infusion syndrome [37], invariably abating clinical and forensic misinterpretation of propofol metabolites [38].

Conclusion

Piroxicam (2.2 mg/kg) and propofol (6 mg/kg) provide good, smooth balanced preanaesthetic medication, increased duration of anaesthesia that lasted for 49.12-54.88 minutes, characterized by decreased heart rate, pulse rate, and decreased respiratory rate, in comparison to piroxicam (4.4 mg/kg) and propofol (6 mg/kg), respectively. Propofol infusion syndrome was prevented by preanaesthetic medication of piroxicam with propofol in Nigerian indigenous dogs.

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Declaration of Conflict of Interest

The authors declare no conflict of interest.

Ethical of approval

The animals were handled according to the guiding principle of animal research as recommended by the Ethical Committee, Department of Veterinary Surgery and Diagnostic Imaging, College of Veterinary Medicine, Federal University of Agriculture, Makurdi, Benue State, Nigeria, given the permit number 2021002.

TABLE 1. Onset of anaesthesia, duration of anaesthesia and duration of surgery

	Time (Minutes)			
Treatment	**Quantity of drug administered (mls)**	**Onset of anaesthesia**	**Duration of anaesthesia**	**Duration of surgery**
Propofol (6 mg /kg) /piroxicam (4.4 mg /kg)	8.6±0.96[a]	1.45±0.91[a]	49.40±5.61[b]	45.60±6.14[b]
Propofol (6 mg /kg) /piroxicam (2.2 mg /kg)	6.66±1.05[b]	0.09±0.02[b]	57.80±3.77[a]	52.00±2.88[a]

Keys: a = significantly higher (p≤0.05) along the column; b =significantly lower (p≤0.05) along the column

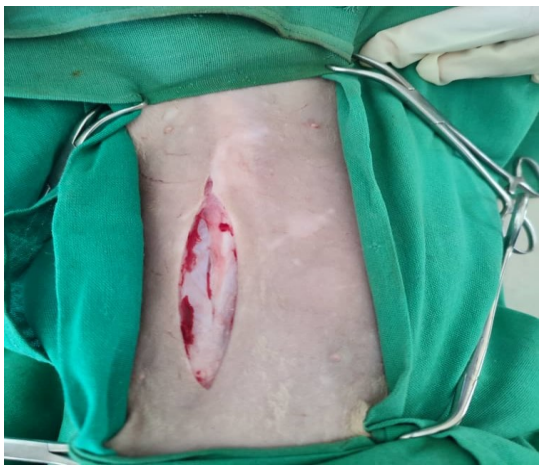

Fig. 1. Ventral midline incision

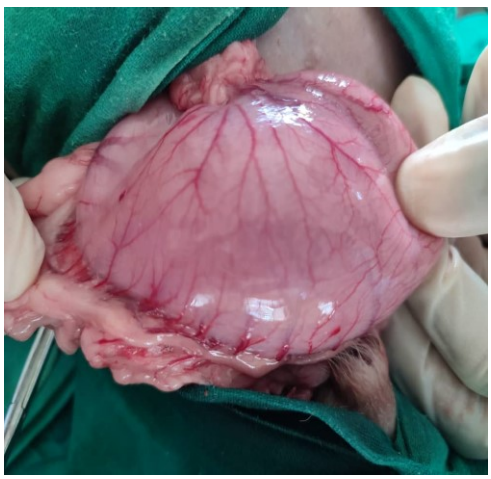

Fig. 2. Exteriorized stomach

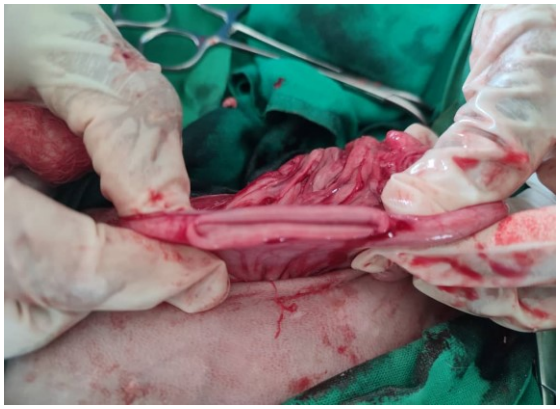

Fig.3. Incision on the stomach

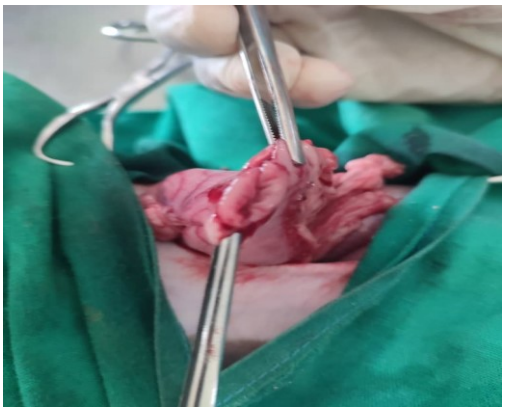

Fig. 4. Exposed mucosa lining of the stomach

Fig. 5. Suture of the skin using horizontal mattress suture pattern

TABLE 2. Effects of piroxicam and propofol on vital parameters of dogs undergoing gastrotomy

Treatment	Vital parameters	Time (hour) 0.0	0.5	3.0	6.0	12.0	24.0
Piroxican (4.4 mg/kg)/ Propofol (6mg/kg)	Rectal Temperature (^{o}C)	38.18±0.38	37.18±0.38	37.34±0.26	37.70±0.13	37.90±0.16	38.30±0.12
Piroxican (2.2 mg/kg)/ Propofol (6mg/kg)	Rectal Temperature (^{o}C)	38.06±0.13	36.98±0.37	37.38±0.24	37.38±0.17	37.24±0.13	38.08±0.08
Piroxican (4.4 mg/kg)/ Propofol (6mg/kg)	Heart rate (beats/minute)	121.2±9.09^{bd}	146.0±3.11^{ac}	118.8±10.03^{bd}	138.4±5.34^{bc}	142.2±10.37^{b}	136.2±6.41^{bc}
Piroxican (2.2 mg/kg)/ Propofol (6mg/kg)	Heart rate (beats/minute)	124.2±9.36^{bc}	129.0±6.93^{ad}	138.8±3.26^{bc}	119.8±7.34^{bd}	128.2±10.67^{b}	124.4±11.02^{bd}
Piroxican (4.4 mg/kg)/ Propofol (6mg/kg)	Pulse rate (beats/minute	107.0±7.73^{bc}	139.0±5.16^{ac}	107.4±10.79^{bd}	117.0±7.24^{bc}	131.6±10.38^{bc}	124.6±9.02^{bc}
Piroxican (2.2mg/kg)/ Propofol (6mg/kg)	Pulse rate (beats/minute	103.6±6.07^{bd}	127.0±6.31^{bd}	130.4±6.18^{ac}	108.2±8.99^{bd}	121.2±10.32^{bd}	112.4±9.37^{bd}
Piroxican (4.4 mg/kg)/ Propofol (6mg/kg)	Respiratory rate (cycles/minute	26.40±3.01^{bd}	24.40±2.98^{b}	28.40±3.54^{ac}	25.20±4.03^{bc}	20.20±4.41^{bc}	17.60±2.86^{bd}
Piroxican (2.2 mg/kg)/ Propofol (6mg/kg)	Respiratory rate (cycles/minute	28.60±3.06^{ac}	23.50±4.19^{b}	23.60±3.82^{bd}	20.40±1.21^{bd}	19.80±3.67^{bd}	24.80±3.09^{bc}

Keys: a = significantly higher ($p \leq 0.05$) along the row
b = significantly lower ($p \leq 0.05$) along the row
c = significantly higher ($p \leq 0.05$) along the column
d= significantly lower ($p \leq 0.05$) along the column

TABLE 3. Concentration of piroxicam administered at 4.4 mg/kg and 2.2 mg/kg in dogs undergoing gastrotomy

Treatment	Time (Hours) 0.0	0.5	3.0	6.0	12.0	24.0
Piroxicam (4.4 mg/kg)	10.65±1.61^{bd}	14.09±1.02^{bc}	16.39±2.37^{bc}	17.17±2.39^{bc}	18.48±2.61^{bc}	24.28±4.73^{ac}
Piroxicam (2.2 mg/kg)	10.83±2.17^{bc}	13.17±0.52^{bd}	14.41±0.55^{bd}	16.99±1.37^{bd}	18.44±1.31^{bd}	23.52±0.94^{ad}

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