A comparison of the pharmacodynamic effects of intravenous ketamine and xylazine to alfaxalone in Mute swans (*Cygnus olor)* presenting to a wildlife veterinary hospital

Abstract

Objective To compare the effects of intravenous (IV) alfaxalone, or ketamine-xylazine, on anaesthetic induction, recovery and cardiopulmonary variables in mute swans.

Study design A randomised, controlled, clinical study.

Animals A group of 58 mute swans.

Methods Swans were given either alfaxalone (10 mg kg^{-1}) (Group A) or a combination of ketamine (12.5 mg kg^{-1}) and xylazine (0.28 mg kg^{-1}) IV (Group KX). Heart and respiratory-rate, end-tidal carbon dioxide and peripheral oxygen saturation were recorded at 5-minute intervals during anaesthesia. Time from anaesthetic induction to intubation, from cessation of isoflurane to extubation, to lifting head, sternal recumbency and absence of head/neck ataxia were recorded. Anaesthetic and recovery quality were scored from 1 very poor to 5 excellent. Data are presented as median (interquartile range). Significance was set at $p < 0.05$.

Results In group A: 44% (12/27) of swans required mechanical ventilation for 2-14 minutes, compared to 3.2% (1/31) of swans in Group KX ($p = 0.0002$). Heart rate was higher in Group A compared to Group KX 146 (127-168) *versus* 65.5 (56-78) beats $minute^{-1}$ respectively ($p < 0.0001$). The isoflurane concentration required to maintain anaesthesia was higher in Group A [2.5% (2.0-3.0%)] than Group KX [1.5% (1.0-2.0%)] ($p = 0.0001$). Time from cessation of isoflurane administration to lifting head was significantly longer in Group A compared to Group KX 12 (9-17) *versus* 6 (4-7.75) minutes respectively, $p < 0.0001$. Anaesthesia quality scores were significantly better in Group KX.4 (4-5), compared to Group A 4 (3-4), $p = 0.0011$, as were recovery scores Group KX 4 [3-5], Group A 2 [2-3], $p = 0.0005$.

Conclusions and clinical relevance Alfaxalone is a suitable anaesthetic induction agent for use in mute swans. In comparison to ketamine/xylazine there is a greater incidence of postinduction apnoea and a higher incidence of agitation on recovery.

Keywords alfaxalone, anaesthesia, ketamine, quality, swan, xylazine

Introduction (Word count 3933)

Mute swans (*Cygnus olor*) are regularly presented for veterinary treatment at private practices and wildlife hospitals in the UK (Routh 2000). Anaesthesia is often required to facilitate diagnostic procedures, gizzard flushing of ingested lead, surgical removal of fishing litter, and treatment of wounds (Routh 2000).

Mask induction with a volatile agent is stressful, with an increased risk of injury to both the bird and staff and a danger of introducing unacceptably high levels of a volatile agent into the working environment (Routh 2000). Use of a tight-fitting face mask to reduce anaesthetic gas pollution may trigger a stress response in waterfowl, possibly due to stimulation of trigeminal nerve receptors in the beak and nares. This may lead to periods of apnoea and bradycardia which will slow or prevent anaesthetic induction (Edling 2006; Mulcahy 2007). For these reasons, injectable drugs are preferred for anaesthetic induction.

The combination of ketamine and xylazine is widely used to produce short acting surgical anaesthesia in domestic and wild animals, including avian species (Ajadi et al. 2009; Al-Sobayil et al. 2009;) although hypoxaemia, hypoventilation and hypercapnia may occur (Paul-Murphy & Fialkowski 2001). Ketamine and xylazine may be used in combination and administered intravenously (IV) to produce 'balanced anaesthesia' in waterfowl (Taylor 1987). This combination provides more rapid induction and smoother recovery than that observed when ketamine is used alone (Sinn 1999) and the sedative and analgesic effects of xylazine are enhanced (Edling 2006). Routh suggests an anaesthetic protocol for mute swans consisting of ketamine (12.5 mg kg^{-1}) combined with xylazine (0.28 mg kg^{-1}) and administered IV via the medial tarsal vein for induction. Endotracheal intubation then allows maintenance of anaesthesia with isoflurane in oxygen (Routh 2000).

The progesterone derivative alfaxalone is a neuroactive steroid anaesthetic. When given at an appropriate dose, administered over 60 seconds, it produces little cardiovascular or ventilatory depression and minimal excitement during induction and recovery in dogs and cats (Muir et al. 2008; Muir et al. 2009). In the UK, veterinarians may use a drug not authorised for use in a particular species, if its use accords with prescribing cascade guidelines (The cascade: prescribing unauthorised medicines, https://www.gov.uk/guidance/the-cascade-prescribing-unauthorised-medicines). The use of alfaxalone is reported in a variety of species across many taxonomic groups including avian species (Smith & Rodriguez-Barbon 2008; Villaverde-Morcillo et al. 2014; Balko et al. 2017; White & Martinez-Taboada 2019). To date, alfaxalone administered IV for the induction of anaesthesia has not been assessed in mute swans.

The purpose of this study was to compare the effects of alfaxalone to a combination of ketamine and xylazine administered IV on the quality of anaesthetic induction, maintenance, and recovery of anaesthesia in mute swans. Anaesthesia was maintained with isoflurane in oxygen. We hypothesized that alfaxalone would be an effective anaesthetic induction agent in mute swans and that physiological variables measured during anaesthesia would be comparable to those measured following induction with ketamine and xylazine.

Methods

A convenience sample of 58 mute swans presented to a UK wildlife hospital over a 15-month period, requiring general anaesthesia for diagnostic tests or surgical treatment, was used for the study. Inclusion and exclusion criteria were set to reflect the clinical caseload, therefore all swans requiring anaesthesia for a clinical procedure were included and no swan requiring anaesthesia for a clinical procedure was excluded. Sample size (minimum 25 swans per group) was calculated based on resting mean heart rates (HR) ± standard deviation (SD) of swans

presenting for clinical examination during this period (https://clincalc.com/stats/samplesize.aspx, α = 0.05, power = 80%). Each animal was then randomly allocated to one of two groups for routine anaesthesia for clinical procedures by flipping a coin: Group KX - ketamine/xylazine (n = 31) or Group A - alfaxalone (n = 27). The coin toss was performed by a colleague who was not involved in data collection.

Swans underwent clinical examination on admission to the hospital and blood samples were submitted to an external laboratory for measurement of lead concentration, as per hospital protocol. The remaining blood sample from each swan was submitted to an external laboratory for manual packed cell volume (PCV) and white blood cell count estimation.

All swans were acclimatised to the hospital environment for at least 24 hours prior to anaesthesia. Immediately prior to anaesthesia each bird was weighed (Professional Large Platform Veterinary Scales, Burtons, UK, calibrated by the manufacturer), and body condition score (BCS) determined by manually palpating the keel (Bird Size-O-Meter, Pet Food Manufacturer's Association, UK). Age (adult or juvenile) was determined by appearance of plumage, with presence of grey feathers (present up to 2 years of age) indicating a juvenile bird and absence of grey feathers indicating an adult (Wildlife Information Network, http://wildpro.twycrosszoo.org, UK). Mute swans are sexually monomorphic, so sex was recorded only for birds undergoing endoscopic examination including direct observation of gonads. In the absence of endoscopic confirmation, sex was recorded as unknown. Resting heart rate (HR) and respiratory rate (f_R), determined by thoracic auscultation and observation of chest excursions, were recorded immediately prior to anaesthetic induction.

All procedures were performed by the same operator, who was not blinded to the drugs used. Group A swans were given alfaxalone (10 mg kg^{-1}; Alfaxan, Jurox UK Ltd, UK) injected IV over 60 seconds via the medial tarsal vein, and in Group KX swans anaesthesia was induced

with a mixture of ketamine (12.5 mg kg^{-1}; Narketan, Vetoquinol UK Ltd, UK) and xylazine (0.28 mg kg^{-1}; Rompun, Bayer, UK) injected over 10 seconds via the medial tarsal vein.

Immediately following administration of drugs, when the swallowing reflex was lost or delayed and jaw tone was sufficiently relaxed to allow full opening of the bill without tension, subjects were intubated with an uncuffed Murphy endotracheal (ET) tube (Rusch Super Safety Clear Cuffed E.T. Tube, Burtons, UK), size 5-6 mm as appropriate. Isoflurane (IsoFlo, Abbot Laboratories Ltd., UK) was administered at a concentration of 0-5%, delivered in oxygen at a flow rate of 200 mL kg^{-1} $minute^{-1}$ via an Ayres T-piece (Modified Ayres T Circuit, Burtons, UK) circuit. The fraction of inspired oxygen (FIO_2) was > 95% throughout anaesthesia for all swans. Time from completion of the anaesthetic induction agent(s) injection to successful tracheal intubation was recorded (seconds). Respiratory rate (f_R), end-tidal carbon dioxide ($PE´CO_2$) and peripheral haemoglobin oxygen saturation (SpO_2) were measured using a multiparameter monitor (Vetronic Vitalstore, Vetronic Services Ltd, UK). The machine used a side-stream capnograph technique (flow rate 50 mL $minute^{-1}$) with the sampling tube attached at the junction between the endotracheal tube and the anaesthetic circuit. The machine was calibrated by the manufacturer immediately prior to despatch for use in this study using a Precision Gas concentration mixture (REF: 755583-HEL, GE Healthcare LTD, UK). It is self-calibrating at each start up, so no user calibration is required. The SpO_2 sensor probe was attached to the bird's tongue. HR was measured by thoracic auscultation. Physiological variables were recorded immediately after intubation and at 5-minute intervals throughout anaesthesia. Plane of anaesthetic was judged by assessment of palpebral and corneal reflex, muscle relaxation and jaw tone. In the event of apnoea (defined for the purpose of the study as failure of spontaneous ventilation for > 30 seconds) manual ventilation was performed at a rate of 2-4 breaths $minute^{-1}$ until spontaneous ventilation resumed. Swans were positioned on a thermostatically controlled electric heat pad (Double Faced Vet Heating Mat, Burtons

Veterinary, UK) calibrated by the manufacturer, and in right lateral recumbency where possible in order to minimise the compressive effects of viscera on abdominal and caudal thoracic air sacs and thus on ventilation. For each subject the duration of anaesthesia (defined as the time between anaesthetic induction and cessation of isoflurane) and the time from cessation of isoflurane to extubation, lifting head, sternal recumbency and absence of head and neck ataxia were recorded. A score of 1-5 (1 = very poor, 5 = excellent), scoring system devised by the author, was recorded for the quality of anaesthesia and quality of recovery for each procedure (Table 1).

Following completion of the diagnostic procedure or treatment, isoflurane administration was discontinued, and oxygen provided until extubation at the point of purposeful head movement. Swans were monitored until they were standing without assistance.

Statistical analyses

Statistical analysis was performed using Minitab Statistical Software (Ver. 17; Minitab, Inc., State College, PA USA; www.minitab.com). Study data were tested for normality (Anderson-darling test). Parametric descriptive statistics were produced for weight data. Other data were non-normally distributed, and the non-parametric Mann-Whitney and Kruskal-Wallis tests were selected for analyses. *p*-value was set at 0.05. Data are displayed as median and interquartile range (IQR).

A Kruskal-Wallis stratification matrix ruled out the influence of lead poisoning, pre-operative medications, reason for anaesthesia, haematological status, sex, BCS life stage, euthanasia outcome and resting HR as confounding variables on the anaesthetic variables measured in the two groups.

Results

Demographic information for swans in each anaesthetic group is provided in Table 2 and reasons for anaesthesia of individuals in each group are summarised in Table 3. Of the original 58 swans, 10 birds in Group A and 7 birds in Group KX were euthanised during anaesthesia as a result of diagnostic findings which would preclude successful rehabilitation and release back into the wild. No additional drugs were administered at induction; however, some swans were currently being treated with meloxicam [0.5-1 mg kg^{-1}, orally (PO), twice daily]; Metacam, Boehringer Ingelheim Ltd, UK) (n = 10/58) and/or amoxicillin-clavulanic acid (125 mg kg^{-1}, PO, BID; Synulox, Zoetis UK Ltd, UK) (n = 7/58) prior to anaesthesia, to treat musculoskeletal disease or superficial wounds. These animals were allocated randomly between groups and stratification analysis confirmed that concurrent medications did not significantly impact the cardiorespiratory variables measures.

Stratification analysis identified just one confounding variable between time to intubate and median f_R. No other variables were identified as confounding. Euthanasia during anaesthesia was excluded as a confounding variable, therefore data from these individuals were retained in the induction and anaesthesia results (Group A - n = 27/58, Group KX - n = 31/58) but not analysed in the recovery results (Group A - n = 17/58, Group KX - n = 24/58). After recovery from anaesthesia, and after completion of this study, an additional seven swans in Group A and 11 swans in Group KX were euthanised. No other complications were noted following the study and the remaining swans were rehabilitated and released to the wild.

All swans were intubated at the first attempt; however, time to intubation was significantly (p = 0.0176) shorter in Group A compared to Group KX. Median f_R was significantly higher in Group A than Group KX at 10 minutes (p = 0.0049) and 15 minutes (p = 0.0010) post anaesthetic induction (Table 4). HR and f_R were measured at 5-minute intervals

throughout anaesthesia; a median value was calculated for each bird and an overall median calculated for each group. The f_R of Group A swans was 13 breaths minute^{-1}, (8-17), which was significantly (p = 0.0306) higher than that of Group KX swans at 10 breaths minute^{-1}, (8-12). However, this result was confounded by the 'time to intubation' variable which was significantly (p = 0.0002) shorter in Group A than Group KX. Swans in Group A, 44% (12/27) required manual ventilation for between 2-14 minutes, compared to 3.2% of swans (1/31) in Group KX; this single swan required manual ventilation for 4 minutes. There were no significant differences between groups in median $P_{E'}CO_2$ or median SpO_2 during anaesthesia.

Physiological variables of swans in Group A and Group KX, prior to and during anaesthesia, are shown in Table 4. Median resting HR was significantly higher in Group A at 92 beats minute^{-1} (80-102) compared with Group KX 88 beats minute^{-1} (72-96) (p = 0.03). There was no significant difference in resting f_R between groups.

The median HR (beats minute^{-1}) during anaesthesia was significantly higher in Group A at 146 beats minutes^{-1} (127-168) than Group KX 66 beats minutes^{-1} (56-78) ($p < 0.0001$). The stratifying analysis of initial HR as a potential confounding variable indicated that median HRs throughout anaesthesia remained significantly different between Group A and Group KX regardless of initial HR.

The isoflurane concentration (Vol%) required to maintain an appropriate level of anaesthesia was significantly (p = 0.0001) higher in Group A 2.5%, (2-3) compared with 1.5% (1.5-2.0) in Group KX. The duration of anaesthesia (minutes) did not differ significantly between groups: Group A was 18 (15-28) and Group KX was 17 (15-27). All swans that recovered from anaesthesia (n = 41/58) did so without complication. Time (minutes) to full recovery from anaesthesia (absence of ataxia or uncontrolled head and neck movements) did not differ significantly between the two groups.

There was a significant difference between groups in time (minutes) from cessation of isoflurane to lifting head: Group A 12 (9-17), Group KX 6 (4-8), $p \leq 0.0001$ (Table 5). There were no further significant differences in recovery times between groups.

Overall, anaesthetic quality score for Group KX was significantly ($p = 0.0011$) higher 4 (4-5) compared with Group A 4 (3-4), the difference primarily attributable to adult swans. The anaesthetic quality score for Group KX adults of 4 (4-5); $n = 21$ was significantly ($p = 0.0019$) higher than that for Group A adults 3 (3-4); $n = 18$. The anaesthetic quality scores for juvenile swans did not differ significantly between Group KX 5 (4-5); $n = 10$ *versus* Group A 4 (3.5-4.5); $n = 9$ $p = 0.0621$. Recovery quality scores differed significantly ($p = 0.0005$) between Group KX [4, (3-5)] and Group A [2, (2-3)] (Table 6).

Discussion

In this study the time to intubation was calculated from the time that each swan had been given its full dose of induction agent through to the time of intubation and it was shorter in Group A than Group KX. The different durations of drug injection may have impacted on this variable, as it was longer for Group A (60 seconds) than Group KX (10 seconds). In human studies, speed of injection of anaesthetic induction drugs significantly influences induction time, for example a slower speed of injection of propofol or etomidate resulted in a slower induction time (Rolly et al. 1985; Gillies & Lees 1989). This contrasts the results of this study in which the faster induction time was recorded with the drug given more slowly. Veterinary studies of the effect of induction agent administration speed are limited, but a study in dogs showed rapid IV administration of either propofol or alfaxalone provided suitable conditions for endotracheal intubation, although time to intubation was not stated (Amengual et al. 2013). Regardless of the difference in time to intubation between groups in our study, both protocols can be considered effective for anaesthetic induction prior to intubation in mute swans.

The decrease in HR following anaesthetic induction in Group KX is probably attributable to the use of xylazine, as bradycardia is a characteristic response to α_2 adrenoceptor agonist drugs (Clarke, 1969). The decrease is similar to that found in mute swans during anaesthesia with propofol (Muller et al. 2011). Conversely, HR increased in the alfaxalone group following induction and this elevation was maintained for the duration of anaesthesia, although the median value for the whole anaesthesia was within the published reference range in this species (Greenacre et al. 2018). Alfaxalone causes a transient increase in HR in dogs immediately following induction, caused by reduced peripheral resistance due to vasodilation (Muir et al. 2008).

Since the 'time to intubation' variable confounded the median f_R variable, the difference in f_R between the two groups could not be empirically attributed to the different anaesthetic protocols, rather than a result of the difference in time to intubation. However, the most probable explanation is that both the shorter time to intubation and the higher f_{Rs} observed in Group A compared to Group KX are a result of the induction agent used.

In many species the most common adverse effects of alfaxalone following induction of anaesthesia are hypoventilation and apnoea, effects related to the dose (Muir et al. 2008 & 2009) and rate of injection (Amengual et al. 2013). This effect was evident in our study where a significantly higher occurrence of postinduction apnoea was observed in Group A (44%) compared to Group KX (3.2%), $p = 0.0002$. Alfaxalone was administered over 60 seconds, as recommended in other species (Grint et al. 2008), therefore speed of injection was not expected to be the cause of the apnoea seen here. During the authorization phase of alfaxalone, clinical trials demonstrated a 44% incidence of postinduction apnoea in dogs and 19% in cats following drug administration (SPC Alfaxan, Jurox UK Ltd, UK). However, the duration of apnoea in the swans of this study was longer than that reported in those dogs and cats. Postinduction apnoea of up to 27 minutes has been reported in rabbits given alfaxalone IV for the induction

of anaesthesia (10 mg kg^{-1}) (Navarrete-Calvo et al. 2014). This may have resulted from both the dose and the rapid rate of drug injection, although the rabbits had been premedicated with morphine, which may have contributed to ventilatory depression.

The dose of 10 mg kg^{-1} we used in this study was based on the available literature (Smith & Rodriguez-Barbon 2008) and personal experience. A similar dose of 10-15 mg kg^{-1} IV is reported in domestic chickens for the induction of anaesthesia (White & Martinez-Taboada 2019). However, lower doses are reported in other avian species such as flamingos (Villaverde-Morcillo et al. 2014) so modifications to the dose and speed of administration would be worth exploring further.

Overall, subjective scores for quality of anaesthesia were 'good' to 'very good' for all swans in the study, but scores were higher in the KX group. When the data were analysed by life stage, the difference in quality of anaesthesia was significant only between the adults in the two groups. Quality of anaesthesia in juvenile swans did not differ significantly between the two groups and was better than in adults. Multimodal anaesthesia and additional premedication should be considered for adult swans where a more invasive procedure is to be performed and alfaxalone is used for the induction of anaesthesia.

Although $P_{E'}CO_2$ readings did not significantly differ between the two groups, these values were higher than expected. Hypoventilation has been documented in a variety of birds anaesthetized with isoflurane (Ludders et al. 1990; Ludders 2001; Paul-Murphy & Fialkowski 2001; Cushing & McClean 2010; Hawkins et al. 2013).

The need for higher doses of isoflurane to maintain an adequate plane of anaesthesia in Group A suggests that KX has a greater isoflurane sparing effect than alfaxalone. Recovery times were similar between groups. Subjective scores for quality of recovery were; however, significantly poorer with alfaxalone. Poor recoveries were associated with wing flapping and

ataxia, in some cases necessitating manual restraint of individuals to prevent self-trauma. In dogs and cats, agitation and hyperaesthesia are reported during the recovery period following the use of alfaxalone for the induction of anaesthesia (Posner & Burns 2009; Jimenez et al. 2012; Mathis et al. 2012;). Muller et al (2011) report excitation in 55% of mute swans on recovery from propofol anaesthesia which ceased within a few minutes. In comparison 47.1% of swans in Group A and 12.5% of swans in Group KX scored a 1 or 2 for recovery quality in our study. Excitation in recovery from alfaxalone anaesthesia is frequently reported in avian species - a study of intramuscular administration of alfaxalone in budgerigars demonstrated excitement on both induction and recovery (Balko et al. 2017). While a study in Quaker parrots also reported excitation on induction, which was attenuated with the addition of midazolam as a premedication (Whitehead et al. 2019). Since excitation in recovery was observed in both groups, we recommend that swans should be observed until fully recovered and gentle manual restraint including wrapping in a towel applied, if excitation occurs.

Use of premedication reduces the excitement seen during induction or recovery (Whitehead et al. 2019), and midazolam is the most widely used avian premedicant (Raftery, 2013). However, the data sheet for alfaxalone (Summary of Product Characteristics, Alfaxan, Jurox UK Ltd, UK) states that the use of benzodiazepines as sole premedicants in dogs and cats prior to alfaxalone may lead to an increased incidence of psychomotor excitation on recovery. Agitation on recovery was reported with the use of midazolam and alfaxalone/alphadalone in Mallard ducks (Machin & Caulkett 1998). Conversely, studies in Bengalese finches (Perrin et al., 2017), Quaker parrots (Whitehead et al., 2019) and other avian species (Kubiak, 2017) suggest that midazolam may be a useful premedicant to reduce excitation in recovery from alfaxalone anaesthesia. Additionally, other premedicants such as butorphanol may be considered (Kubiak, 2017, Perrin et al., 2017).

All swans other than those that were euthanased, recovered from anaesthesia without complication. Several swans were subsequently euthanased on welfare grounds as they were unable to be released, either due to a deterioration in clinical condition or development of complications related to rehabilitation. Stratification analysis showed that a decision to euthanase an individual at any stage of the study and in either treatment group did not have a significant effect on the results, and so euthanasia of these birds was unrelated to the anaesthetic agent used. Prior to anaesthesia, some swans with pre-existing disease were treated with analgesics or antibiotics. Stratification analysis indicated that these drugs did not significantly affect the results. Alternatively, an untreated painful condition and its physiological consequences, could have been confounding variables (Hellyer et al. 2007).

Analysis of 'real-life' clinical data may reflect clinical caseloads more closely but may also include confounding factors that can influence the variables of interest. Stratification as described by Kahlert (Kahlert et al., 2017) was used in this study to identify any confounding relationships between the anaesthetic and cardiopulmonary variables of interest and incidental demographic or clinical factors. Using this method, the data set is divided into manageable subsets (strata), with each stratum corresponding to the levels of potential confounders e.g., age group, reason for anaesthesia, euthanasia outcome, haematological status etc. The overall cross-tabulation for the association between an exposure and an outcome (e.g., a 2 × 2 table for 'Induction agent group' and 'General anaesthesia quality score') is compared with stratum-specific (e.g., age group) cross-tabulations, and it becomes evident whether one variable confounds another variable. In this study two confounded variables were identified - the 'time to intubation' variable confounded the median f_R variable.

This study has some limitations: it compared two induction drug protocols in a sample of swans admitted to a wildlife hospital. These results may not be directly applicable to a healthy swan population. However, since most swans undergoing anaesthesia do so as part of

a clinical investigation, the results of this study are relevant to the population of swans entering veterinary practice. The study was not a blinded study so operator bias with respect to subjective assessments of anaesthesia cannot be excluded. However, the data we obtained provides useful information about the pharmacodynamic effects of these drugs in the mute swan. Physiological variables were objectively measured using standardised monitoring equipment, minimising operator bias.

Conclusion

Alfaxalone at a dose of 10 mg kg^{-1}, administered IV over 60 seconds, produced smooth and rapid induction of anaesthesia in the mute swan, adequate for endotracheal intubation. A period of apnoea was observed following alfaxalone administration so manual ventilation should be provided. Ataxia and agitation may be seen during recovery, necessitating manual restraint in some cases. Adult swans anaesthetized with alfaxalone may benefit from the use of an additional muscle-relaxing pre-medication.

Alfaxalone is a suitable anaesthetic induction agent in mute swans. In comparison to KX there is a greater incidence of postinduction apnoea and a greater incidence of agitation on recovery.

References

Ajadi RA, Kasali OB, Makinde AF, Adeleye AI, Oyewusi JA, Akintunde OG (2009) Effects of midazolam on ketamine-xylazine anesthesia in Guinea fowl (*Numida meleagris galeata*). Journal of Avian Medicine and Surgery 23, 199–204.

Al-Sobayil FA, Ahmed AF, Al-wabel NA, Al-Thonayian AA, Al-Rogibah FA, Al-Fuaim AH, Al-Obaid AO, Al-Muzaini AM (2009) The use of ketamine, xylazine and isoflurane for induction and maintenance of anaesthesia in ostriches (*Struthio camelus*). Journal of Avian Medicine and Surgery 23(2), 101-107.

Amengual M, Flaherty D, Auckburally A, Bell AM, Scott EM, Pawson P (2013) An evaluation of anaesthetic induction in healthy dogs using rapid intravenous injection of propofol or alfaxalone. Veterinary Anaesthesia and Analgesia 40, 115-123.

Balko J, Lindemann D, Chinnadurai S (2017) Evaluation of the anesthetic and cardiorespiratory effects of intramuscular alfaxalone compared with isoflurane inhalant and manual restraint in the budgerigar (*Melopsittacus undulates*). Veterinary Anaesthesia and Analgesia 44(5), 1262.

Clarke KW, Hall LW (1969) "Xylazine"--a new sedative for horses and cattle. Veterinary Record 85(19), 512-517.

Cooke SW (1995) Swan anaesthesia. The Veterinary Record 136(18), 476.

366 Cushing A, Mcclean M (2010) Use of thiafentanil-medetomidine for the induction of
367 anesthesia emus (*Dromaius novaehollandiae*) within a wild animal park. Journal of Zoo and
368 Wildlife Medicine 41(2), 234-241.
369
370 Edling TM (2006) Updates in anaesthesia and monitoring. In: Clinical avian medicine volume
371 II. Harrison GJ, Lightfoot TL (eds). Spix Publishing Inc., Palm Beach, Florida. pp. 747-760.
372
373 Gillies GWA, Lees NW (1989) The effects of speed of injection on induction with propofol. A
374 comparison with etomidate. Anaesthesia 44, 386-388.
375
376 Greenacre CB, Luna GL, Morishita TY (2018) Backyard Poultry and Waterfowl. In: Exotic
377 Animal Formulary (5^{th} edn). Carpenter JW, Marion CJ. (eds). WB Saunders. pp.415.
378
379 Grint NJ, Smith HE, Senior JM (2008) Clinical evaluation of alfaxalone in cyclodextrin for the
380 induction of anaesthesia in rabbits. The Veterinary Record 163(13), 395-396.
381
382 Hawkins MG, Malka S, Pascoe PJ, Solano AM, Kass PH, Ohmura H, Jones JH (2013)
383 Evaluation of the effects of dorsal versus lateral recumbency on the cardiopulmonary system
384 during anesthesia with isoflurane in red-tailed hawks (*Buteo jamaicensis*). American Journal
385 of Veterinary Research 74(1), 136-43.
386
387 Hellyer P, Rodan I, Brunt J, Downing R, Hagedorn JE, Robertson SA (2007) AAHA/AAFP
388 pain management guidelines for dogs and cats. Journal of Feline Medicine and Surgery 9, 466-
389 480.
390

391 Jimenez CP, Mathis A, Mora SS, Brodbelt D, Alibhai H (2012) Evaluation of the quality of the
392 recovery after administration of propofol or alfaxalone for induction of anaesthesia in dogs
393 anaesthetized for magnetic resonance imaging. Veterinary Anaesthesia and Analgesia 39, 151-
394 159.
395
396 Kahlert J, Gribsholt SB, Gammelager H, Dekkers OM, Luta G, (2017) Control of confounding
397 in the analysis phase - an overview for clinicians. Clinical epidemiology, 9**,** 195-204
398
399 Kubiak M (2017) Anaesthetic choice in avian patients. Companion Animal, 22**,** 44-49.
400
401 Ludders JW (2001) Inhaled anesthesia for birds. In: Recent advances in veterinary anaesthesia
402 and analgesia: companion animals. Gleed RD, Ludders JW (eds). International Veterinary
403 Information Service, Ithaca, New York.
404
405 Ludders JW, Mitchell GS, Rode J (1990) Minimal anaesthetic concentration and
406 cardiopulmonary dose response of isoflurane in ducks. Veterinary Surgery 19(4), 304-307.
407
408 Machin KL, Caulkett NA (1998) Investigation of Injectable Anaesthetic Agents in Mallard
409 ducks (*Anas platyrhynchos*): A Descriptive Study. Journal of Avian Medicine and Surgery
410 12(4), 255-262.
411
412 Mathis A, Pinelas R, Brodbelt DC, Alibhai HIK (2012) Comparison of quality of recovery
413 from anaesthesia in cats induced with propofol or alfaxalone. Veterinary Anaesthesia and
414 Analgesia 39, 282-290.
415

Muir W, Lerche P, Wiese A, Nelson L, Pasloske K, Whittem T (2008) Cardiorespiratory and anesthetic effects of clinical and supraclinical doses of alfaxalone in dogs. Veterinary Anaesthesia and Analgesia 35(6), 451-462.

Muir W, Lerche P, Wiese A, Nelson L, Pasloske K, Whitte T (2009) The cardiorespiratory and anesthetic effects of clinical and supraclinical doses of alfaxalone in cats. Veterinary Anaesthesia and Analgesia 36(1), 42-54.

Mulcahy DM (2007) Free-living waterfowl and shorebirds. In: Zoo animal and Wildlife Immobilisation and Anesthesia. West G, Heard D, Caulkett N (eds). Blackwell Publishing. pp. 299-324.

Muller K, Holzapfel J, Brunnberg L (2011) Total intravenous anaesthesia by boluses or by continuous rate infusion of propofol in mute swans (*Cygnus olor*). Veterinary Anaesthesia and Analgesia 38, 286-291.

Navarrete-Calvo R, Gomez-Villamandos RJ, Morgaz J, Dominguez JM, Fernandez-Sarmiento A, Munoz-Rascon P, Lopez Villalba I, Del Mar Granados M (2014) Cardiorespiratory, anaesthetic and recovery effects of morphine combined with medetomidine and alfaxalone in rabbits. The Veterinary Record 174(4), 95.

Paul-Murphy J, Fialkowski J (2001) Injectable anaesthesia and analgesia of birds. In: Recent advances in veterinary anaesthesia and analgesia: companion animals. Gleed RD, Ludders JW. (eds). International Veterinary Information Service, Ithaca, New York.

Pet Food Manufacturer's Association, https://www.pfma.org.uk/_assets/docs/pet-size-o-meter/pet-size-o-meter-birds.pdf. Last accessed 12th January 2021.

Posner LP, Burns P (2009) Injectable anaesthetic agents. In: Veterinary Pharmacology and Therapeutics (9th edn) Riviere JE, Papich MG. (eds). Wiley-Blackwell. pp. 265-299.

Raftery A (2013) Avian anaesthesia. In Practice 35, 272-278.

Rolly G, Versichelen L, Huyghe L, Mungroop H (1985) Effect of speed of injection on induction of anaesthesia using propofol. British Journal of Anaesthesia 57(8), 743–746.

Routh A (2000) Veterinary care of the mute swan (*Cygnus olor*). In Practice 22, 426-443.

Sinn LC (1999) Anaesthesiology. In: Avian Medicine: Principles and applications. Ritchie BW, Harrison GJ, Harrison LR (eds.) HBD International, Delray Beach, Florida. pp.1066-1080.

Smith S, Rodriguez-Barbon A (2008) Waterfowl: medicine and surgery. In: Manual of farm pets. Roberts V, Scott-Park F. (eds). BSAVA Quedgeley, Gloucester. pp. 250-273.

Taylor M (1987) Avian anaesthesia, a clinical update. Proceedings of the 1st International Conference on Zoological and Avian Medicine (AAV/AAZV). pp. 519-524.

The cascade: prescribing unauthorised medicines, https://www.gov.uk/guidance/the-cascade-prescribing-unauthorised-medicines. Last accessed 17th March 2020.

Villaverde-Morcillo S, Benito J, Garcia-Sanchez R, Martin-Jurado O, Gomez De Segura IA (2014) Comparison of isoflurane and alfaxalone (alfaxan) for the induction of anesthesia in flamingos (phoenicopterus roseus) undergoing orthopaedic surgery. Journal of Zoo and Wildlife Medicine 45(2), 361-366.

White DM, Martinez-Taboada F (2019) Induction of Anesthesia with Intravenous Alfaxalone in two ISA Brown Chickens (*Gallus Gallus Domesticus*). Journal of Exotic Pet Medicine 29, 119-122.

Whitehead MC, Hoppe SM, Musser JMB, Perkins JL, Lepiz ML (2019) The Use of Alfaxalone in Quaker Parrots (*Myiopsitta monachus*). Journal of Avian Medicine and Surgery 33(4), 340–348.

Wildlife Information Network. http://wildpro.twycrosszoo.org. Last accessed 12th February 2020.