The Influence of a Combined Butorphanol and Midazolam Pre-medication on Anaesthesia in Psittacid Species

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Introduction

Use of anaesthesia in birds

In veterinary medicine, anaesthesia is used in all species to induce a lack of sensibility to noxious stimuli and to immobilise patients. General anaesthesia induces a controlled depression of the central nervous system to induce hypnosis, lead to immobility and reduce pain perception.

Avian species maintained in captivity frequently resent restraint and manipulation, and forced restraint can lead to significant stress to the patient. In fractious animals this also risks injury to both bird and handler. Many procedures that may be carried out in conscious domestic animals, such as blood sample collection, a thorough clinical examination and microchip placement, often require anaesthesia in avian patients to minimise stress and facilitate handling. In addition, any painful procedures and surgical interventions also require anaesthesia with appropriate analgesia.

Use of pre-medicants in domestic species

In domestic animal practice balanced anaesthesia is advocated, with a combination of drugs administered to result in an unconscious state, provide analgesia and lead to muscle relaxation. The use of multiple agents allows a lower dose of each to be administered than if a single agent was used alone. This aims to avoid the marked physiological changes associated with administering a high dose of a single anaesthetic agent and so reduces the likelihood of negative adverse effects that are expected at high doses of many anaesthetic agents.

The use of premedication is advised to:

- Reduce stress and anxiety experienced by the patient
- Facilitate patient handling
- Reduce the dose of induction and maintenance agents required
- Reduce pain sensation
- Improve the quality of recovery[38]

Exact pre-medication agents used vary depending on patient factors, procedure to be carried out, pre-existing health concerns and availability of specific drugs. The ideal premedication combination

provides sedation, anxiolysis, analgesia and has minimal effects on the cardiovascular and respiratory function of the patient. In most situations a sedative agent plus an analgesic will be administered to attempt to meet these criteria.

Use of pre-medicants in avian anaesthesia

The use of pre-medicant agents in avian anaesthesia is not in frequent practice for various reasons. An important factor is a relative lack of data for pre-medicant protocols. Although the same benefits of a balanced anaesthetic regime could potentially apply to avian patients, there is less published evidence to support the safety and benefits of pre-medication. Concerns about possible adverse effects of unfamiliar regimes combined with a familiarity and confidence with existing gaseous anaesthetic protocols maintains the status quo.
However, a pre-medicant has particular advantages in management of anxiety in these patients and has potential benefits, as in domestic species, of balanced anaesthesia, provision of analgesia, reduced induction time, reduced doses of maintenance agents and smoother induction and recovery periods. Data is sparse, but available for some agents and the use of pre-medicants and sedative regimes in avian species has been documented in peer-reviewed articles.

Use of inhalant anaesthesia alone

The use of isoflurane as a sole anaesthetic agent for general anaesthesia in avian species is common practice. It is economical and has the benefit of not relying on organ function for excretion as elimination is predominantly by exhalation, though some hepatic metabolism occurs. As it is moderately soluble, rapid changes in depth of anaesthesia are possible and volatile delivery systems required necessitate oxygen administration. Isoflurane administered to give a surgical plane of anaesthesia gives fair muscle relaxation and less myocardial depression than halothane. Induction is rapid (1-2mins) at a concentration of 3-5% and recovery is generally fast though there seems to be a direct relationship between total anaesthetic time and recovery time[17]. Compared with other gas anaesthetics, isoflurane is minimally cardiac depressive and is associated with a decreased incidence of cardiac arrhythmias when compared with other volatile agents[60].

However, isoflurane and other volatile agents are not without adverse qualities. Induction is unpleasant for the patient due to the irritant vapour and aversive smell, and an excitation phase can develop during induction. Sevoflurane is preferable for induction as it is less irritating to mucous membranes, but costs are significantly higher than for isoflurane. Volatile anaesthetic agents are

also associated with a dose-dependent range of negative cardiovascular side effects including induction of arrhythmias, bradycardia and hypotension[5,21]. Inhalant anaesthetics act as respiratory depressants with increased significance at higher doses, and this group of anaesthetics also appears to produce greater respiratory depression in birds compared to mammals[21].

The minimum alveolar concentration (MAC) is the concentration of anaesthetic gas that renders immobile 50% of patients subjected to a painful stimulus, giving a guide for requirements for levels required for achieving a surgical plane of anaesthesia. The concentration of volatile agent which results in apnoea is known as the anaesthetic index (AI). In avian species, MAC and AI are close when volatile agents are used as sole anaesthetics. This similarity means that close monitoring of anaesthetic depth is critical to prevent excessive depth and a resulting apnoea[21]. Assisted or controlled ventilation is often necessary to manage apnoea and maintain oxygenation during long procedures.

Volatile agents also provide minimal or no analgesia. During anaesthesia with these agents, neurological function is depressed and conscious pain perception is prevented but this does not provide true analgesia[13]. Depth of inhalant anaesthesia required to permit painful procedures is associated with significant cardiovascular and respiratory depression, and neuronal wind-up is unlikely to be avoided[15]. Used alone, inhalant anaesthetics are not adequate for any procedure that could potentially cause pain. In fact, inhalation anaesthetic agents can actually trigger hyperalgesia at low concentrations, which are unavoidably created at both induction and recovery. This has been suggested as a cause of violent recoveries in birds due to perceived intense pain as isoflurane levels decrease[40]. This occurs with enhancement of activity of unmeyelinated C-fibres and can be managed with avoidance of painful stimuli or provision of appropriate peri-operative analgesia[72].

There are also clinician risk factors to consider with volatile agent usage. Isoflurane is administered via a face mask initially, exposing both bird and handler to gas. Handler exposure is reduced by using a well-fitting mask and diaphragm, and aided by an efficient scavenging system, but some leakage is still likely to occur. At mask removal for intubation the residual vapours are unavoidably released. Due to the anatomy of the avian air sac system, coelomic surgery or orthopaedic surgery involving pneumatised bones also allows for escape of anaesthetic gas into the environment.

In most cases of anaesthesia induction an excitation phase will occur and so Isoflurane is administered at a high concentration (4-5%) to reduce induction time and shorten the excitation period. Once the bird is unresponsive then the isoflurane concentration is reduced to maintenance levels (2-3%) and the bird is intubated. This approach needs very close monitoring as overdose is easily achieved at high concentrations.

Use of injectable agents

In domestic species it is uncommon to use inhalant agents alone, except in neonatal or moribund patients. Often a pre-medication of a sedative and analgesic is followed by intravenous injection of the induction agent with intubation and subsequent administration of oxygen and a volatile agent.

Use of injectable agents alone in birds for is also not ideal as most injectable anaesthetic agents exhibit dose-dependent cardiovascular and/or respiratory depression and effects across species are not necessarily predictable, leading to variable responses. Elimination of injectable agents relies on metabolism of the active products and hepatic or renal clearance so the recovery period can be protracted or turbulent.Use of injectable agents also means that clearance is governed by organ function so anaesthetic depth cannot be quickly modified, though some anaesthetic drugs have specific antidotes. In avian species, injectable anaesthesia is usually reserved for situations where inhalant anaesthesia is not practical, such as in-field situations.

Role of premedication in avian anaesthesia

An appropriate pre-medicant followed by inhalant anaesthesia may provide a middle ground. A carefully chosen premedication protocol can ameliorate some of the negative aspects of isoflurane anaesthesia by providing analgesia, improved muscle relaxation and decreasing the isoflurane dose required, thereby reducing its negative cardiovascular and respiratory effects. If a sedative or anxiolytic is used in the pre-medication then the excitation phase at induction may be reduced and anxiety associated with handling and administration of noxious volatile agents better controlled. Short, calm induction improves handler safety, both from reduced risk of injury and the lessened exposure to volatile agents. There is also the possibility of induction using a gradual increase in isoflurane if the excitation phase is not present, reducing the risk of inadvertent overdose. There is not reliance on injectable agents alone to achieve a surgical plane of anaesthesia, so the dose of the injectable agent is reduced and hence the cardiovascular effects and clearance times are proportionally reduced and safety is improved.

Consideration of Sedative agents in psittacines

An ideal pre-medicant in psittacines would include a sedative to facilitate handling and reduce induction time. An agent with anxiolytic properties would be preferred to reduce patient stress both facilitating handling and as part of the analgesic management as it has been suggested reduced anxiety can decrease CNS activity and contribute to reduced pain perception[8]. A number of agents are in common use in domestic animal species but not all are equally appropriate for avian patients.

Ketamine

Ketamine is a dissociative anaesthetic, leading to CNS depression and lack of pain sensation. It is frequently used in domestic species, especially in cats and rabbits, where it leads to reliable sedation in combination with other agents. Ketamine alone is not recommended for dogs due to association with seizure activity [53].

Ketamine is hepatically metabolised and excreted by the kidneys. It causes variable hypertension, dose-dependent cardiac and respiratory depression and increased muscle tone. Ketamine provides hypnosis and analgesia but is not suitable as a sole anaesthetic agent due to the lack of muscle relaxation, risk of seizure induction and prolonged, turbulent recovery associated with high doses. Ketamine can be combined with an α2-agonist or benzodiazepine to reduce dose requirements, which reduces the cardiac and respiratory depression and shortens the recovery time.

Ketamine and $\alpha-2-$agonist combinations have been used for field anaesthesia in avian species. A regime of 4-10mg/kg combined with 0.15-0.35mg/kg medetomidine, given by intramuscular injection is reported to give 20minutes of anaesthesia in raptors[19]. Subsequent reversal of the medetomidine with atipamezole leads to birds standing within ten minutes but also reverses the analgesia of the medetomidine component. Lower doses are reported for pigeon anaesthesia, of 1.5-2mg/kg ketamine with 0.060-0.088mg/kg medetomidine, again by intramuscular injection[14]. This combination is not recommended for birds with renal or cardiac pathology due to the induction of a marked medetomidine-induced hypotension[19]. Ketamine has been reported to be ineffective in some groups of birds, incuding penguins, gallinules, water rail, Golden pheasant, toucans and hornbills[19]. Ketamine combinations are an option for sedation or anaesthesia of birds but have

significant potential for cardiorespiratory compromise and prolonged recovery with excitation and incoordination.

Alpha-2 agonists

$\alpha-2-$agonists such as xylaxine and medetomidine bind to inhibitory adrenergic receptors within the sympathetic nervous system leading to analgesia, sedation, muscle relaxation, anxiolysis and a subsequent reduction in induction agent requirements[38].

Al-Sobayil (2009) administered Xylazine for pre-medication in ostriches at 4mg/kg but little sedation resulted. Xylazine is not recommended as a sole agent or at high doses due to significant hypertension and bradycardia and also gastrointestinal side effects such as diarrhoea and regurgitation[3].

Medetomidine is a reliable sedative in domestic species, without triggering excitation and can be fully reversed by atipamezole. Side effects include bradycardia, vomiting and an initial hypertension followed by hypotension. Sandmeier (2000) evaluated the potential of medetomidine for sedation in pigeons (*Columbia livia*) and yellow crowned Amazons (*Amazona ochrocephala ochrocephala*), but high doses of 1.5-2mg/kg produced insufficient sedation for dorsal recumbency to be maintained and lead to a reduction in both cardiac and respiratory rates.

$\alpha-2-$agonists are more suitable when used in combination with agents such as ketamine for sedation or anaesthesia. However, lack of reliable sedation and cardiovascular and respiratory depression make $\alpha-2-$agonists a suboptimal option for pre-medication.

Alfaxalone/alfadalone

Alfaxalone and alfadalone are steroid anaesthetic combinations that can be given by intravenous or intramuscular injection. Historic preparations were associated with anaphylaxis in dogs and, less frequently, in cats. Good muscle relaxation, fast induction, rapid hepatic metabolism and renal excretion and mild cardiorespiratory depression render this a theoretically useful agent for birds. Doses of 5-10 mg/kg IV or 20-40 mg/kg IM are reported for short duration anaesthesia in birds, with the intravenous route preferred due to the pain associated with intramuscular injection of a large volume of the solution[14]. Fatal adverse reactions have been reported in red-tail hawks (*Buteo jamaicensis)*, and psittacines (including lories and lovebirds) so use is not advisable[19]. A newer aqueous solution of alfaxalone is now available but needs further evaluation before it can be incorporated into avian anaesthetic protocols.

Propofol

Propofol is a substituted phenol anaesthetic for intravenous administration only. It has a rapid, smooth induction phase, fast clearance and little accumulation making it extremely useful in sedation or anaesthetic induction in waterfowl. The diving response exhibited in this group hinders gaseous agent administration via face mask in conscious animals, but easily accessible medial tarsal veins allow intravenous injections. When given rapidly to effect for induction, propofol produces a marked respiratory depression with apnoea frequently resulting. Hawkins (2003) showed that with a constant rate infusion (CRI) of 1mg/kg/min in red tailed hawks (*Buteo jamaicensis*) and Great horned owls (*Bubo virginanus*), a slow induction was achieved without resulting apnoea but recovery was prolonged, with excitation. It is not convenient for anaesthesia in psittacine species as intravenous access is not always possible in conscious parrots without significant restraint, leading to stress, risk of bird or handler injury and hyperthermia.

Benzodiazepines

Benzodiazepines are frequently used as pre-medicants and sedatives in human and small animal anaesthesia. They exert their actions at a specific benzodiazepine receptor on post-synaptic nerve endings within the central nervous system[16]. This receptor is part of the gammaaminobutyric-acid (GABA) complex and binding increases availability of the inhibitory neurotransmitter, glycine, causing sedation, anxiolysis and muscle relaxation.

They are hepatically metabolised and recognised to reduce doses of other anaesthetic drugs, as part of balanced anaesthesia. Benzodiazepines have no intrinsic analgesic properties so are frequently combined with opioids or $\alpha-2-$agonists for analgesia and enhanced sedation. They can be antagonised with flumazenil.

DIAZEPAM

Diazepam is insoluble in water and is best administered intravenously due to pain and unreliable absorption seen with intramuscular injection. This renders it less suitable for psittacine patients.

MIDAZOLAM

Midazolam is a water-soluble benzodiazepine which can be administered via intramuscular injection without pain or irritation. It is a more potent sedative than Diazepam[37]. Intramuscular injection leads to peak sedation at 10-15mins with a duration of 1-1.5hrs in domestic species[38]. Following hepatic transformation, the metabolites are inactive so effects are short-lived. Midazolam is considered the benzodiazepine of choice in small animal anaesthesia. Administered alone it has little/no sedative effect so is combined with other agents for premedication in healthy animals, or used alone for debilitated patients or those with cardiorespiratory compromise[38]. However, if administered as a sole agent in cats, midazolam can cause ataxia, dysphoria and excitation, making handling more difficult[29].

Midazolam has little effect on the cardiorespiratory systems though mild, transient hypertension, bradycardia and hypoxia have been reported in humans[70].

Midazolam is described as the gold standard for premedication in paediatric human patients due to its fast onset, effective sedation, lack of delayed recovery from anaesthesia and anxiolytic properties[59]. Avian patients share many of the concerns for anaesthetists with anxiety and resistance associated with restraint and facemask induction, tendency towards hypothermia and potential for respiratory depression under anaesthesia. Desirable pre-medicant qualities are similar for both psittacine and paediatric human patients with anxiolysis, smooth induction and recovery, analgesia and lack of cardiorespiratory depression being paramount. Sinha (2012) compared midazolam and butorphanol as single agent pre-medicants in children and the cohort administered midazolam had superior anxiolysis at induction.

Midazolam has been used in avian species for sedation by intramuscular injection and more recently by intranasal administration. Administration by intramuscular injection has been demonstrated to cause no significant changes in cardiopulmonary function in Canada geese, pigeons and quail[64,62,12]. Adjadi et al (2009) assessed the effect of adding 0.3mg/kg midazolam into a ketamine/xylazine anaesthetic protocol in Guinea fowl (*Numidia meleagris*). Those administered midazolam had faster onset of anaesthesia, markedly improved analgesia, lower respiratory rates and no appreciable variation in heart rate or temperature from the group given xylazine/ketamine alone. Regurgitation was however observed in the midazolam administered group.

Intranasal midazolam has been investigated as a minimally invasive way to administer pre-medication or sedation and shows promise for low-restraint delivery. 12.5–15.6mg/kg administered

via pipette into the nostrils of canaries (*Serinus canaria)* was effective in producing sedation[65], as was 12-14mg/kg in zebra finches (*Taeniopygia guttata*)[7]. Administration of 6.5+/-1mg/kg intranasal midazolam in pigeons (*Columbia livia)* gave sedation with fast onset of 3minutes post-administration and 23.4+/-3.7minutes recumbency, with 82.0+/-6.2minutes sedation in total. Recovery was reported to be good with birds alert and feeding afterwards[70]. 2mg/kg midazolam administered intranasally to Hispaniolan Amazons (*Amazona ventralis*) gave similar findings of sedation within 3minutes of administration, produced reduced vocalisation and defence responses on handling and was effectively reversed with intranasal flumazenil[41]. In ring-necked parakeets (*Psittacula krameri)* midazolam administered intranasally at 7.3mg/kg, induced marked sedation within 3minutes and recovery was complete within 2-3hrs with birds active and feeding, whereas other combinations (detomidine, midazolam/ketamine and xylazine/ketamine) lead to protracted recovery periods[66].

Consideration of analgesic agents in Psittacines

All vertebrates share similar neuroanatomic and neuropharmacologic pathways for nociception so it is presumed that birds perceive pain in similar ways to mammals. Presence of pain affects animals psychologically and physiologically and so a reduction in pain is desirable not only for patient welfare, but also to enhance healing, maintain normal homeostatic mechanisms, and reduce recovery time[69].

Analgesia is of particular importance in pre-medication as provision of analgesia before any noxious stimulus is important in minimising pain perception. Trauma to tissues induces changes in the central nervous system that result in sensitisation to pain and reduced response to analgesia administered subsequently. Prior provision of analgesia prevents sensitisation and neuronal wind-up, reducing post-operative pain. Dyson (2008) states that "the ideal approach to managing pain in these patients is to prevent it, and this usually starts with the premedication analgesics". In birds this is even more critical than in domesticated species as prey species typically mask pain symptoms. To demonstrate pain would establish vulnerability for an observing predator. As a result clinical judgement of when analgesia is required is more difficult in birds. Often post-operative pain has to be assumed based on likely tissue insult rather than overt symptoms.

α–2–agonist/ketamine combinations

α-2-agonist s in combination with ketamine provide some analgesia but this is insufficient for painful procedures. This lack of pain relief is exacerbated with α2-agonist reversal. Adaji et al (2009) reported that the addition of midazolam to a xylazine/ketamine anaesthesia improved analgesia and hypnosis in Guinea fowl but slowed recovery.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs act by inhibition of cyclooxygenase (COX) enzymes. COX-2 suppression was historically believed to reduce prostaglandin production, blocking inflammatory pathways and preventing chemical production of inflammation and pain. COX-1 activity interference was thought to lead to side effects such as disruption of renal perfusion and gastric mucosa replacement. However, the distinction of activity of each enzyme is not as simple as originally thought and there is some overlap of function with side effects possible even with highly specific COX-2 inhibitors[23]. With decimation of

Asian vulture populations following ingestion of cattle treated with diclofenac, there are concerns about the safety of NSAIDs in Old World vultures in particular, and safety and effective dose rates of many NSAIDs in avian species in general are poorly documented.

MELOXICAM

Meloxicam is a COX-2 preferential NSAID, and is twelve times more effective against COX-2 than COX-1[30], It is well absorbed orally and has been demonstrated by Naidoo (2008) to have a short elimination time and produce no adverse effects in Old World vultures. In a clinical trial by Wilson GH(2004), ring neck parakeets (*Psittacula krameri*) administered 0.5mg/kg showed no evidence of side effects but in a study of budgerigars (*Melopsittacus undulatus*) by Pereira(2004), repeat administration of 0.1mg/kg lead to minor histological changes in the glomeruli though serum uric acid levels were unchanged. It would appear from pharmacokinetic analysis that meloxicam pharmacokinetics vary between avian species and allometric scaling and extrapolation do not provide a true basis for determining dosing regimes[32].

CARPROFEN

Carprofen has conflicting data on COX specificity with one study by Kay-Mugford (2000) finding it 1.75 times more selective for COX-2 than COX-1, and another by Wilson JE (2004) finding it five times more selective for COX-2. Both studies were conducted using canine cells so selectivity in avian species is even less clear. In clinical trials, 1mg/kg carprofen significantly improved mobility and manoeuvring of lame broiler chickens confirming a likely analgesic effect in birds as for mammals[43].

Both meloxicam and carprofen have been used widely in avian species and are used peri-operatively to ameliorate analgesia. However, neither is suitable specifically for pre-medication as they lack the additional benefits required such as sedation, anxiolysis or a reduction in anaesthetic agent doses.

Corticosteroids

Corticosteroids such as betamethasone, prednisolone and dexamethasone are used in mammals for their anti-inflammatory and immunosuppressive effects. In mammals cell-mediated immunity of T-lymphocytes is significantly suppressed but humoral activity of B-lymphocytes is less affected. Overall, corticosteroids disrupt leucocyte activity and chemical signalling leading to reduced immunocompetence and decreased inflammation. Administration of corticosteroids to birds leads to suppression of both cell-mediated and humoral immunocompetence. These effects impair wound healing and predispose to secondary infections. Monocyte suppression is pronounced so infections that require a monocytic response for defence are more likely to develop. Glucocorticoid

administration has been associated with development of Aspergillosis in many species, including pigeons (*Columbia livia*) and budgerigars (*Melopsittacus undulatus)*[25]. Glucocorticoids are also noted in birds to cause hepatocellular damage, abnormalities of growing feathers and suppression of endogenous corticosteroids[39]. Due to the acute and severe side effects, corticosteroids are not advisable for analgesia in avian species.

Opioids

Opioids are used for traumatic, visceral and surgical pain control, and as part of balanced anaesthesia in human and veterinary medicine. They are frequently used in pre-medications to provide analgesia and improve the reliability and intensity of sedation achieved with accompanying agents.

Opioids can be full agonist, partial agonist, mixed agonist/antagonist and full antagonist agents. The distinctions are made based on their ability to induce an analgesic response when bound to central opioid receptors. Agonists have a linear dose-response curve but agonist/antagonists have a dose-response curve that plateaus and higher doses provide no additional analgesia. The distinction between opioid types may be further confused as one opioid may act as an agonist at one receptor type, but a partial agonist or antagonist at a different receptor type. Differences in receptor type, binding and distribution may explain the variation of opioid analgesic effects between species.

Opioid receptor types appear consistent across mammals in the brainstem and spinal cord but may vary in the forebrain and midbrain. There is less information published on avian opioid receptors. Mansour (1988) evaluated opioid receptor distribution and type in pigeons using radiolabelling, showing that κ- and δ-receptors were more prevalent than μ-receptors, with 76% of opioid receptors in the forebrain being of κ-type. The true significance of this is not confirmed but this proportional alteration of opioid receptors may explain why birds seem to have a better analgesic response to κ-agonist opioids than μ-agonists. However, may be an oversimplification as Concannon(1995) suggests that birds may not have distinct μ and κ receptors, or that the avian μ and κ receptors have similar functions.

There are few pharmacokinetic and pharmacodynamics studies completed evaluating opioid use in psittacine species, further complicating an informed selection of an appropriate opioid.

FENTANYL

Fentanyl is a μ-opioid agonist that has been evaluated by Hoppes (2003) in umbrella cockatoos (*Cactua alba*) for analgesia. Doses of 0.02mg/kg IM did not affect response to thermal and electrical

noxious stimuli despite maintaining fentanyl plasma levels at those considered efficacious in humans for a period of at least 2hrs. 0.2mg/kg by subcutaneous injection did lead to analgesia but also produced transient hyperactivity and required a large injection volume so was not recommended for routine analgesia. Pavaz (2010) looked at using an intravenous constant rate infusion of fentanyl in red-tailed hawks (*Buteo jamaicensis*) which reduced the minimum anaesthetic dose of isoflurane by 31-55% and had no significant effects on heart rate, blood pressure and blood gas analysis but the CRI approach has not yet been utilised in psittacines.

MORPHINE

Morphine has been demonstrated by Concannon(1995) to have a dose-dependent isoflurane-sparing effect in chickens subjected to a nociceptive stimulus. As a result morphine was determined to have an analgesic, sedative or muscle relaxant effect. The chickens in this study were subjected to intermittent positive pressure ventilation so effects of morphine on respiration were undetermined but blood pressure and heart rate were unaffected. Morphine maybe a suitable opioid but further studies are necessary to assess the analgesic effects in psittacines and to evaluate effects on cardiorespiratory parameters when used as part of an anaesthetic protocol.

BUPRENORPHINE

Buprenorphine is a partial μ-agonist with complicated κ-activity as both agonist and antagonistic effects have been reported at κ-receptors. Consistent analgesic demonstration is lacking. Paul-Murphy (2004) showed that 0.1mg/kg IM in African greys (*Psittacus erithacus*) did not produce analgesia, despite subsequent pharmacokinetic analysis showing that this dose produces serum levels analogous to analgesic levels for humans.

BUTORPHANOL

Butorphanol is a mixed agonist/antagonist that has low activity at μ-receptors and strong agonist activity at κ-receptors which has lead to suggestions that it is an appropriate opioid for avian species based on receptor selectivity. Adverse effects seen in mammals, such as dysphoria, have not been reported in avian species. Butorphanol provides poor analgesia in domestic mammals but is particularly useful in enhancing sedation when used alongside benzodiazepines or α–2–αγονιστ s. It has less cardiovascular compromise than pure opioid agonists but can cause a reduction in heart rate and mild decreases in arterial blood pressure secondary to an increase in parasympathetic tone via vagal stimulation[52]. It does not produce dose-related respiratory depression in comparison to μ-agonists and respiratory depression is not seen at standard dose rates in mammals[38].

Analgesic efficacy has been demonstrated by Paul-Murphy (1999) in psittacines, with a demonstrable reduction in withdrawal effect inAfrican greys (*Psittacus erithacus erithacus, P. e. timneh*) following administration of 1-2mg/kg butorphanol. Analgesia in Hispaniolan Amazons (*Amazona ventralis*) required a higher dose of 3mg/kg. Analgesic effect and prevention of a CNS 'wind-up' has been described in pigeons, with those that received butorphanol before orthopaedic surgery showing a faster return to normal activity and behaviour than those receiving postoperative butorphanol only[49].

Butorphanol appears to have a short elimination time in avian species, with Riggs (2008) suggesting a likely dosing interval of 2-4hrs in great horned owls (*Bubo virginianus*) and red-tailed hawks (*Buteo jamaiscensis*)to maintain plasma levels at a concentration expected to produce analgesia. A pharmacokinetic study by Sladky (2006) in Hispaniolan Amazons (*Amazona ventralis*)showed low serum levels 2hrs after 5mg/kg IM suggesting relatively fast elimination also occurs in psittacines.

Butorphanol has been suggested as part of a balanced anaesthesia protocol for psittacine species. Curro (1994a, 1994b) found that the Isoflurane MAC was significantly reduced in African grey parrots (*Psittacus erithacus*) and cockatoo species that were administered 1mg/kg IM. The reduction in isoflurane requirement was most marked in cockatoos with 25% MAC reduction and less striking in the African grey parrots, with 11% MAC reduction. There was no significant isoflurane-sparing effect in blue-fronted Amazons (*Amazona aestiva*) suggesting species variation in dose requirements.

Klaphake (2006) showed that use of butorphanol as a pre-medicant (at 2mg/kg) in Hispaniolan Amazons produced no change in intubation time, extubation time or recovery. There was a brief reduction in respiratory rate compared to the control group but no hypoxia or hypercapnoea, and there was a significant decrease in the concentration of sevoflurane required for anaesthesia. Pre-operative dosing rates were suggested to be 1-3mg/kg .

Butorphanol appears be a suitable agent for pre-medication with its analgesic properties, apparent safety, minimal cardiovascular effects, and anaesthetic sparing effect. Its relatively short elimination time may be of benefit as there is not a prolonged sedative effect post-anaesthesia.

Use of A Combination of Midazolam and Butorphanol for Pre-Medication

Midazolam and butorphanol is a well-established pre-medicant combination used in critical canine and feline cases (ASA grades 3-5)[38]. It provides variable sedation, and minimal cardiorespiratory compromise[38]. In humans, the combination of midazolam and an opioid leads to enhancement of opioid analgesia.

In domestic cats, midazolam/butorphanol combinations have poor sedative effect, and an associated cardiorespiratory compromise and so ketamine or an α-2-agonist combination is preferred for premedication or sedation in healthy cats[6,20]. In domestic dogs, midazolam/butorphanol combinations provide mild-moderate sedative effects with minimal cardiorespiratory depression. Kojima (1999a, 1999b) compared midazolam/butorphanol with medetomidine/midazolam and acepromazine/butorphanol combinations in domestic dogs and found that midazolam/butorphanol produced the least cardiovascular effects. It was noted that sedation produced with the midazolam/butorphanol combination was more variable between patients.

Of particular relevance is a study by Mutoh (2002) which looked at the effects of three pre-medicant combinations on mask induction of anaesthesia using sevoflurane, providing a parallel with the induction approach used for avian patients. Dogs that had received a combined midazolam/butorphanol pre-medicant demonstrated a shorter induction time and milder changes in heart rate, mean arterial blood pressure, cardiac output, and respiratory rate, compared to those undergoing mask induction without pre-medicants.

Effects of a midazolam/butorphanol combination have been evaluated in other species. Schroeder (2011) reported that this combination in rabbits lead to sedation, progressive hypothermia and respiratory depression with a resulting mild hypoxaemia. The midazolam dose of 2mg/kg used in this study is higher than those generally used in clinical practice and the authors suggested that a reduction in dose may ameliorate the negative effects observed on respiration during this study.

Dzikiti (2009) evaluated the effects of pre-medication on propofol induction of anaesthesia in goats. The combination of midazolam/butorphanol resulted in a 38.1% reduction in the dose of propofol required for induction but gave unreliable sedation. Cardiovascular and blood gas parameters were within accepted reference ranges and showed no significant difference when compared to

acepromazine, midazolam, butorphanol or combined acepromazine/butorphanol pre-medicants, or when compared to the saline control group.

Sinha (2012) compared midazolam and butorphanol as single agent pre-medicants in children undergoing elective surgery. It was found that both provided sedation and anxiolysis but the cohort administered midazolam had superior anxiolysis at induction and those administered butorphanol showed less evidence of post-operative pain and required rescue analgesia less frequently. A combination of both agents may give preferable anxiolysis and analgesia while maintaining negligible effects on cardiorespiratory function.

Application in avian patients

Benzodiazepines and opioids (particularly butorphanol) have been used to provide sedation or anxiolysis for captive birds and there has been recent interest in these agents for sedation of birds for non-invasive procedures[21,36,65,70]. The published material provides background information on dosing regimes, patient response and safety.

Sedation using a combination of butorphanol and midazolam has been described by Lennox(2011) with doses of butorphanol at 1–3 mg/kg and midazolam, at 0.25–1.0 mg/kg given by intramuscular injection for sedation. Macaws were described to respond less profoundly to midazolam/butorphanol combinations with adequate sedation not being achieved with doses that had proven effective in other species. Importantly, the author states that no adverse effects were associated with the use of this combination for pre-medication or sedation in psittacine species in a three year period of regular usage. Abou-Madi (2001) described a similar protocol but with lower doses using butorphanol at 0.4-1mg/kg and midazolam at 0.1–0.5 mg/kg, both by intramuscular injection.

The combined characteristics of butorphanol and midazolam together achieve the aims of pre-medication, chiefly anxiolysis, muscle relaxation, sedation, and a reduction in the dose of other anaesthetic agents required. Doses of 0.5mg/kg midazolam and 1mg/kg butorphanol were selected as these were within the ranges reported as successful by Lennox (2011) and Abou-Madi (2001), and the butorphanol dose was within the range reported as effective for analgesia by Paul-Murphy (1999), as isoflurane-sparing by Curro (1994) and without adverse effect as a pre-medicant by Klaphake (2006).

Evaluation of Effects of Butorphanol and Midazolam on Cardiorespiratory Parameters

Both agents used for premedication were selected based on characteristics of minimal effect on cardiorespiratory parameters. However, as with all anaesthetic agents they have been associated with effects on anaesthetic parameters in birds or other species and anaesthetic monitoring is crucial in detecting and reacting to cardiovascular or respiratory changes in order to maintain stable anaesthesia.

Butorphanol has been associated with dose-related respiratory depression in dogs, and mild decreases in arterial blood pressure and heart rate[52,58] but therapeutic doses in domestic mammals appear to have little clinical effect on cardiovascular parameters. In a retrospective analysis by Hofmeister (2008) of the effect of butorphanol on cardiopulmonary parameters in equine anaesthesia, it was concluded that butorphanol at 0.02mg/kg lead to no significant changes in blood pressure, heart rate, end tidal CO_2 ($ETCO_2$), or SpO_2 when used as part of balanced anaesthesia. Where administered as a direct response to increased heart rate or elevation of blood pressure during surgery, butorphanol assisted in deepening the plane of anaesthesia and lowering these parameters. However, in an earlier study by Stick (1989), at higher doses of 0.2mg/kg in equids, butorphanol was found to induce hypotension.

Biermann (2012) demonstrated that a combination of butorphanol and midazolam in domestic cats caused a mild decrease in arterial blood pressure, elevation of heart rate and caused agitation rather than sedation. However, cardiac depression seen with midazolam/butorphanol was mild and significantly less marked than combinations that utilised α-2-agonists.

Midazolam is frequently selected for cardiac, respiratory or critical patients for sedation or premedication as it has little cardiorespiratory compromise. However, it can increase the effects of other agents used so could potentiate the cardiovascular effects of butorphanol or isoflurane. Midazolam has been associated with mild, transient hypertension, bradycardia and hypoxia in human patients[70]. No significant cardiovascular effects have been reported in avian species[3,64], but monitoring of blood pressure, heart rate and pulse oximetry will assist in detection of any significant changes.

RESPIRATORY MONITORING

Respiratory rate declines progressively as anaesthesia depth increases leading to apnoea which, if not corrected, is followed by cardiac arrest. Respiration in birds is reliant on body wall muscles as there is no internal diaphragm to assist with air movement. Deep anaesthesia with associated suppression of muscular activity therefore has a direct effect on respiratory performance. This is exacerbated when birds are placed in dorsal recumbency and the combined weight of the keel and pectoral muscles compromises excursive respiratory movements. Reduced movements lead to a decreased tidal volume and less efficient carbon dioxide excretion. Intermittent positive pressure ventilation to maintain Oxygen saturation (spO_2) above 90% and $ETCO_2$ between 35-45 mmHg is advocated where respiratory movements are likely to be compromised[24].

Capnography

Even when respiration appears normal in rate and movements, there can still be an undetected respiratory acidosis. Measuring $ETCO_2$ using capnography has been shown by Edling (2006)to be effective approximating arterial CO_2levels in African grey parrots (*Psittacus erithacus*), although the $ETCO_2$ reading consistently overestimated arterial CO_2 by 5mmHg. Arterial blood gas sampling may be preferable for true evaluation of presence of respiratory acidosis but arterial access, sample volume required and limited availability of analytic equipment limit the suitability of this method in general practice.

Pulse oximetry

Commercial pulse oximeters are not calibrated for birds and the readings may be inaccurate. Due to different absorption characteristics of avian haemoglobin the pulse oximeter values may read below the true saturation levels[26]. Schmidt (1998) concluded that pulse oximetry is not a reliable means of evaluating oxygenation in avian species. However, pulse oximeter readings may still be of value in following trends in apparent oxygenation in avian patients and as an indirect indicator of peripheral perfusion. The probe can be placed on cloacal or oral mucosa, or on a featherless area of skin.

CARDIAC FUNCTION

Heart rate can be monitored with auscultation using a stethoscope, ECG monitoring or an oesophageal stethoscope.

Direct blood pressure monitoring is the gold standard, but arterial size, artery accessibility, increased anaesthetic time and cost of equipment often precludes use in general practice. Use of indirect methods is easier; equipment is present in most practices, arterial access is not required and measurement is typically accomplished quickly. Zehnder (2009) found that the Doppler method of measuring indirect blood pressure was a better approximation of mean arterial pressure in red tailed hawks (*Buteo jamaicensis*), than oscillometric methods. Acierno (2008) however found little agreement between direct and Doppler indirect readings measured in anaesthetised Hispaniolan Amazon parrots (*Amazona ventralis*), casting doubt on reliance upon this parameter. However, as for pulse oximetry, the absolute value may be questionable but trends in blood pressure in individuals still provide information on changes in cardiovascular function and remain useful where direct methods are not feasible.

TEMPERATURE

Avian patients are typically small with a high surface area to volume ratio and a high metabolic rate. This predisposes to heat loss and hypothermia is a common sequel to anaesthesia. Thermal support is needed throughout anaesthesia and recovery; otherwise anaesthetic recovery may be delayed. Flexible probes inserted into the oesophagus are suggested to be the most accurate method for monitoring core temperature. Cloacal probes are not a true reflection of core temperature[46].

Materials And Methods

Aim of the study

In light of the lack of published material clearly demonstrating the effects of pre-medication in psittacine birds, a controlled study was designed to directly assess the effect of a butorphanol/midazolam pre-medication on anaesthesia. As this study utilised in birds presenting independently for anaesthesia for therapeutic or diagnostic reasons, and both anaesthetic regimes compared are considered as appropriate for use in psittacines (Lennox, 2011), no Home Office licence was necessary.

Methods

Sample

Birds included in this study were those reported by their owners as healthy and with no abnormalities evident on clinical examination. They underwent general anaesthesia for elective routine procedures, namely microchip placement, a hormone implant placement (Suprelorin, Virbac UK), grooming procedures or routine health screens. Birds that demonstrated any abnormalities on clinical examination or subsequent tests were excluded from the study. This amounted to one bird (a female African grey parrot) with hepatomegaly on radiography, leucopaenia on haematology and was seropositive for *Chlamydophila psittaci*.

The seventeen birds consisted of eight African greys (*Psittacus erithacus*), Two orange winged Amazons (*Amazona Amazonica*), One double yellow headed Amazon (*Amazona oratrix*), Three blue and gold macaws (*Ara arauana*), two Hahn's macaws (*Diopsittaca nobilis*) and one umbrella cockatoo (*cacatua alba*). Birds ranged from four months of age to 15 years (where age was known) with a mean age of 5.94 years when the five birds of unknown age were excluded. Three birds had been sexed as male, two as female, the rest were of unknown sex.

Procedure

Birds were initially presented by owners for procedures and were admitted following physical examination, including cardiac and respiratory auscultation and weight measurement.

All parrots were hospitalised in a specific psittacine ward at 30˚C and provided with food and water based on their normal diet type.

Birds were randomly allocated by the theatre nurse into one of two groups:

1. Test group (P): Each bird was administered a pre-medicant of 0.5mg/kg midazolam (Hypnovel, 5mg/ml,) and 1mg/kg butorphanol (Torbugesic, 10mg/ml, Fort Dodge) combined and diluted to 0.25ml with 0.9% saline (Aquapharm) into the left pectoral muscle by intramuscular injection.

2. Control group (NP): Each bird was administered 0.25ml saline into the left pectoral muscle

The veterinary surgeon specified the appropriate dose of butorphanol and midazolam for the bird's weight, prepared and labelled two injections (one of pre-medicant and one of saline) for each bird. The veterinary nurse responsible for injecting the bird was the only person aware which group the bird had been allocated to and which injection had been administered. The veterinary nurse monitoring the anaesthesia and the veterinary surgeon were not informed until completion of the anaesthetic and recording data to avoid bias.

15minutes after injection, the bird was presented to the anaesthetist and veterinary surgeon for the designated procedure wrapped in a towel. Anaesthesia was then induced via facemask administration of 5% Isoflurane (IsoFlo, Abbott Animal Health, UK) in 2l/min oxygen. A clear plastic facemask connected to a non-rebreathing system of an Ayres T-piece was used, attached to a passive scavenging system. Once induced and intubated, isoflurane concentration was lowered as appropriate to maintain anaesthesia. Patients were maintained on a heat pad for thermal support – the same design of heat pad was used in each case, heated to the same temperature prior to use.

<u>Measures</u>

The template used for recording the following parameters is included in Appendix 1.

- Duration of induction

The time from initial exposure to isoflurane until the bird was unconscious with no voluntary movements, a slow palpebral reflex and endotracheal intubation was possible without resistance was recorded.

- Quality of induction

This was subjectively scored by both observers on a scale of 1-5:

1. No struggling/avoidance behaviour
2. Minor avoidance behaviour (random head and body movements), no vocalisation

3. Purposeful attempts to move away from mask
4. Repeated escape attempts and vocalisation
5. Bird difficult to restrain, wing flapping, struggling and vocalisation

Physiological parameters were recorded throughout anaesthesia:

- Isoflurane concentration

This is the concentration of isoflurane required for maintaining lateral recumbency with a slow but present palpebral reflex. The percentage was recorded every minute from the vaporiser setting.

- Indirect blood pressure

This was recorded every 5 minutes. An appropriately sized cuff (width approximating 40-50% circumference of limb) was placed around the distal humerus. The Doppler sensor was placed over the superficial ulnar artery on the medial aspect of the elbow. The cuff was inflated and the pressure required to occlude arterial flow recorded from a sphygmomanometer. The propatagial soft tissue was not found to impede measurements in a when pectoral and pelvic limb readings were compared by Zehnder(2009).

- End Tidal Carbon Dioxide

The $ETCO_2$ reading was recorded from values generated from the capnograph every minute.

- Oesophageal temperature

A flexible thermometer was placed into the oesophagus and readings recorded every two minutes.

- Respiratory rate

Respiratory excursions were observed and breaths per minute recorded every two minutes.

- Heart rate

The heart was auscultated using a stethoscope over the craniolateral coelom and the heart rate was recorded every two minutes.

- Pulse oximetry

A pulse oximeter clip was attached to the propatagium of the left wing and the generated value for oxygen saturation recorded every two minutes.

- Extubation time

Following completion of the procedure, the isoflurane vaporiser was switched off, the anaesthetic circuit reservoir bag emptied and the time taken to extubation recorded. Extubation was carried out when the bird began making purposeful head movements.

- Perching time

Immediately after extubation the bird was moved to a ward heated to 30˚C and placed in a recovery cage. The recovery cage contained a perch positioned at a height of 6 inches above the cage base. The time taken from extubation to stable perching was recorded.

- Recovery quality

The recovery quality was subjectively scored by both observers on a scale of 1-5:

1. No excitement
2. Mild excitement with poorly co-ordinated movements
3. Struggling and vocalisation
4. Short periods of rolling and wing flapping
5. Continuous flapping, rolling and vocalisation

Following completion of all data entry, the person responsible for preparing the premedication or saline then recorded on the monitoring form which group the bird had been allocated to.

Data analysis

Data was inputted from the recording sheets and analysed using Microsoft Excel and SPSS (version 19).

Results

No apnoea or cardiac irregularities were noted in any of the birds in the study and no complications arose from the anaesthesia or procedures carried out. All birds were discharged to their owners the same day with normal behaviour, appetite and activity.

When presented to the anaesthetist enclosed in a towel, no difference was perceptible in any of the birds apart from the Umbrella cockatoo who appeared markedly sedated with closed eyes and a reduced response to handling.

Tables 1 and 2 document the anaesthetic parameters recorded for birds administered saline and birds administered midazolam/butorphanol.

Data screening

The normality of the data distributions was considered to determine whether parametric tests were appropriate for the data set (see Appendix 2, histograms).

The distributions of the following outcome variables were considered to be normal and therefore appropriate for parametric tests:

- Duration of induction
- Isoflurane concentration
- Respiratory rate
- Temperature drop
- Blood pressure
- Mean end tidal carbon dioxide
- Peak end tidal carbon dioxide
- Extubation time

The following outcome variables did not show a normal data distribution and were therefore analysed using non-parametric tests:

- Heart rate
- Pulse oximetry
- Perching time

As the subjective score measures of induction and recovery quality do not yield interval or ratio level data, non-parametric tests were used for these outcome variables. Independent samples tests were used in order to establish whether there was a significant difference between the treatment and control group on all variables.

Variables suitable for parametric analysis were analysed using an independent samples *t* test, variables suitable for non-parametric analysis were analysed using a Mann Whitney U test.

Means and standard deviations for each of the outcome variables suitable for parametric analysis, and the median for each of the outcome variables suitable for non-parametric analysis are shown in Appendix 3.

TABLE 1

TABLE 2

Induction time

The induction time of the birds in the treatment group (*M*=64.88) was significantly lower than that of the birds in the control group (*M*=98.00), $t(15) = 2.20$, $p<0.05$. This represents a small to medium effect $r=0.49$.

Induction quality

Scoring of the induction appeared consistent with identical scores given by both observers in 13 of 17 birds. In the remaining four birds, all were in the control group and a single point difference in the paired scores was recorded. Where scores were not equal, the mean value of the different scores was used in subsequent analysis. In the test group induction scores were identical in all birds.

The mean induction score allocated to the birds in the treatment group (Mdn=1.00) was significantly lower than that of the birds in the control group (Mdn=2.50),$U=9.5$,$z=-2.60$,$p<0.01$. This represents a large effect $r=0.63$.

Isoflurane requirements

The mean isoflurane concentration for the birds in the treatment group (*M*=2.28) was significantly lower than that of the birds in the control group (*M*=3.02),$t(15)=2.69$,$p<0.05$. This represents a large effect $r=0.57$.

Cardiovascular parameters

The heart rate of birds in the treatment group (Mdn = 210) did not differ significantly from that of birds in the control group (Mdn =204),$U=31.0$,$Z=-0.481$,$p>0.5$

The blood pressure was recorded in five of the control group and seven of the test group. Where multiple values were recorded during the anaesthetic, the mean value was used for comparison. The mean blood pressure values in the treatment group (*M* =163.4) did not differ significantly from that of birds in the control group (*M*=199.5),$t(10)=1.003$,$p>0.05$

Respiratory parameters

The respiratory rates in the treatment group (*M* =25.58) did not differ significantly from that of birds in the control group (*M* =31.78),$t(15)=0.953$,$p>0.05$

Pulse oximetry was recorded for seven of the control group and seven of the test group. The pulse oximetry values of birds in the treatment group (Mdn =99.25) did not differ significantly from that of birds in the control group (Mdn =99.83),U=14 ,Z =-1.348,p>0.05

Mean end tidal carbon dioxide levels were recorded for seven of the control group and eight of the test group. The mean $ETCO_2$ levels of birds in the treatment group (M =37.76) did not differ significantly from that of birds in the control group (M =38.47),t(13)=0.137,p >0.05

Peak end tidal carbon dioxide levels were recorded for seven of the control group and eight of the test group. The peak $ETCO_2$ of birds in the treatment group (M =55.04) did not differ significantly from that of birds in the control group (M =55.86),t(13)=0.061,p >0.05

Presence of pedal reflex

A withdrawal response to a manual toe pinch was noted in seven of the nine birds in the control group. In all birds with a positive response this was initially seen immediately after induction at the start of general anaesthesia. In two birds a reflex was also present at one subsequent time point, and in one bird at two subsequent time points.

Within the test group, only two birds of the eight demonstrated a positive withdrawal response, one immediately after induction, and one at 2 minutes into anaesthesia.

Temperature

As anaesthetic length varied from 5minutes to 18minutes depending on the procedure, the birds undergoing longer anaesthetics would be expected to experience a greater reduction in temperature. To allow a more balanced comparison of temperature loss, the temperature drop per minute was calculated to take this into account.

The temperature drop of birds in the treatment group (M =0.14) did not differ significantly from that of birds in the control group (M = 0.15),t(15)=0.148,p>0.05

As would be expected, the two smallest birds (the Hahn's macaws NP8 and P7) had the greatest calculated temperature drop per minute of 0.28 and 0.23˚C/min respectively.

Extubation

The time taken for extubation of birds in the treatment group (M =144.13) did not differ significantly from that of birds in the control group (M =95.67),t(15)=-1.750,p>0.05

Recovery quality

Scoring of the recovery period appeared consistent with identical scores given by both observers in 12 of 17 birds. In the remaining five birds, two were in the control group and three were in the test group and only a single point difference in the paired scores was recorded. In all cases or disagreeing scores, the scores given were 1 and 2, or 2 and 3, suggesting that the lower scores were not clearly demarcated preventing definitive allocation in some cases.

The recovery quality of birds in the treatment group (Mdn =2.00) did not differ significantly from that of birds in the control group (Mdn = 2.00),U=34.5,Z=-0.148,$p>0.5$

Time taken for recovery from anaesthesia to stable perching

There was an increase in time taken to achieve stable perching for the birds in the test group (Mdn =450.50) but the difference was not considered statistically significant to the values from the control group (Mdn =280.00),U=22.00,Z =-1.347,$p>0.05$

Comparison of data from old world and new world parrots

Tables 3 and 4 show the parameters recorded for old world parrot species, and Tables 5 and 6 show values recorded for new world species.

Comparison of the old world parrots and new world parrots allocated to the test group was carried out.

Induction time showed a clear difference, with a mean values for old world parrots of 44.75 (±11.12)s and new world parrots of 85.00 (±26.22).

A greater time from extubation to perching was seen in the old world group, with a mean time taken of 704.50 (±429.46)s compared to a mean time of 323.75 (±150.34)s in the new world group.

No statistical analysis was carried out to assess differences between the subdivided test group due to lack of statistical power in such small sample sets.

Table 3

Table 4

Table 5

Table 6

Discussion

No adverse effects were noted in the control group or in the group administered the butorphanol/midazolam pre-medicant. All birds were discharged to their owners the same day in good health and no concerns were subsequently reported by their owners.

Although regurgitation was highlighted as a potential side effect of midazolam administration in a study in guinea fowl[3], no productive regurgitation was identified in the test group. However, two patients (NP8 and P6) showed vertical head bobbing behaviour and open beak movements in the recovery period consistent with nausea or gastrointestinal discomfort. As one patient (NP8) was in the control group and one (P6) in the test group this behaviour was considered related to anaesthesia as a whole and not directly applicable to the midazolam administration. Both of these birds were macaw species, and no similar behaviour was noted in other birds.

Intubation time was significantly reduced in birds administered pre-medication. Klaphake (2006) found no change in induction time in Amazon parrots administered pre-operative butorphanol suggesting that the Midazolam alone acts to reduce induction time, or acts synergistically with butorphanol. This reduction in time reduces patient and handler isoflurane exposure, reduces duration of stressful stimuli during induction and indicates a degree of anaesthetic sparing effect of the pre-medicant. Induction quality scores were also lower in pre-medicated birds, indicating less patient excitation on induction. This may be due to either sedative or anxiolytic effects of the pre-medicant components, or a combination of both. With a shorter, smoother induction, a sequential approach to isoflurane administration could be used. For this, the bird is started on oxygen via face mask and the isoflurane concentration is gradually increased until anaesthesia is achieved. Isoflurane overdose risk is much reduced compared to a constant high level, reducing the severity of the cardiovascular effects of isoflurane administration. In birds without pre-medication this approach leads to a longer induction time and a prolonged excitation phase but it has been suggested as a method for inducing pre-medicated or sedated birds due to the reduced negative aspects with reduction of excitation following pre-medication[21].

The isoflurane concentration required to maintain anaesthesia was lower in the pre-medicated group. No surgical procedures were carried out so no significant pain would be expected to be experienced by any of the birds in this study. As a result, variation in isoflurane concentration required to maintain anaesthesia should not have been affected by the procedure. A mean reduction in isoflurane concentration of 24.5% was noted, with a 29.6% reduction in Old world

parrots and an 18.2% reduction in New world parrots. Previous studies by Curro (1994a,b), administering 1mg/kg butorphanol to psittacines identified a 25% reduction of Isoflurane MAC in cockatoos, an 11% MAC reduction in African greys and no significant reduction in blue-fronted Amazons (*Amazona aestiva*). In African greys, comparing five African greys in the control group with three in the test group, a 17.8% reduction in MAC was calculated, suggesting an increase in isoflurane-sparing effects of 1mg/kg butorphanol when combined with 0.5mg/kg midazolam. When comparing the Amazon parrots, two individuals in the control group and one in the test group, a reduction in isoflurane requirements was identified at 42.2% but this figure is based on a very small sample group so accuracy is not validated and further numbers are needed to assess whether addition of midazolam does consistently lead to a significant reduction of isoflurane requirements in Amazon parrots.

As with other studies, no significant variation in cardiovascular or respiratory parameters was identified and repeated measurements of SpO_2 and indirect blood pressure gave consistent readings in individuals supporting some degree of reliability for comparison even if exact figures did not necessarily reflect oxygen saturation levels and direct blood pressure values. Blood gas analysis and direct arterial pressure readings would provide a more accurate reflection of respiratory and cardiovascular responses but were not available.

The withdrawal response to a toe pinch was present in 77.8% of the control group and 25% of the test group. Lack of a toe pinch response in a far greater proportion of pre-medicated birds at an apparently similar plane of anaesthesia indicates either an effective sedative or analgesic effect of the pre-medication.

Temperature loss was consistent across both the control and the test group. Some variation was however noted with size of bird. As would be expected, the two smallest birds (the Hahn's macaws NP8 and P7, weighing 136g and 174g) had the greatest calculated temperature drop per minute. This was markedly faster temperature reduction than that which was reflected in values for the medium to large birds. Smaller individuals, with a higher surface area to volume ratio and higher metabolic rate are expected to lose body heat, primarily by convection, at a faster rate than larger individuals under the same conditions.

There was an increase in the time taken from the end of anaesthesia until conscious movements were noted and extubation was carried out in the test group, but the difference was not statistically significant either across test and control groups, or when data was subdivided into old and new

world species. Again the time taken from extubation until birds were perching steadily was prolonged in the pre-medicated group but this difference was not statistically significant.

Looking at the control group alone, there was no consistent increase in recovery time following longer exposure to isoflurane, however the procedures carried out in this study were short in length and anaesthesia length only varied from 5 to 18 minutes in duration so a large variance was not established and subtle differences in recovery time were not identified.

Data from old world and new world parrots was compared. The old world parrots are geographically determined and include those from Africa, Asia, Europe and Australasia, such as African greys and cockatoo species. New world parrots originate from the Americas, including Amazon and macaw species. A number of reports indicate that new world species require higher doses of analgesia or sedative than those that produce clinical effects in species found in the Old world. Macaws have been described by Lennox (2011) to respond less profoundly to the sedative effects of midazolam/butorphanol combinations than old world species and Curro (1994a,b) showed no isoflurane-sparing effect in blue-fronted Amazons (*Amazona aestiva*) though significant reductions were seen in cockatoos and African greys. In addition, 1-2mg/kg butorphanol has been demonstrated by Paul-Murphy(1999) to provide analgesia in African greys (*Psittacus erithacus erithacus, P. e. timneh*) but Hispaniolan Amazons (*Amazona ventralis*) required a higher dose of 3mg/kg butorphanol.

The old world parrots given pre-medication showed a shorter induction time, lower isoflurane concentration and increased perching time compared to the new world parrots. These results are supportive of a greater effect of butorphanol/midazolam on old world parrots compared to new world parrots. Further comparison of larger numbers at family or species level would also assist in determining whether effects were statistically significant and consistent across subfamilies Psittacinae (including African greys) and Arinae (including Amazon and Macaw species), or varied at species level.

It is recognised that this is a small test group and as such the results should be considered as part of a pilot study to assess effects of pre-medication in psittacines. Effects have been shown to be small, but demonstrate the benefits of pre-medication in the induction phase, both in improvements in terms of speed and quality of induction, and by reducing the isoflurane concentration required to maintain anaesthesia. In addition cardiovascular and respiratory parameters were not significantly different to those of the control group, indicating that negative effects on cardiac and respiratory function are unlikely to result. Though recovery times were slightly longer in pre-medicated birds,

there was no evidence of reduction in recovery quality and all birds were able to be discharged on the same day. The findings of this study support the use of pre-medication in routine anaesthesia of healthy psittacines to improve induction quality, reduce perception of painful stimuli and decrease isoflurane requirements in anaesthesia maintenance. It is hoped that the demonstration of a safe and effective dosing regimen will encourage transfer of the balanced anaesthetic approach into avian practice.

Further work to be carried out includes recruitment of larger numbers of cases to assess the impact scores of areas of where significant differences were identified such as reductions in induction time and isoflurane concentrations. Greater sample size would also help to determine whether statistical significance is achieved in parameters where trends were noted in this study but statistical significance was not confirmed. Extubation time and perching time need wider data collection, as both appeared increased in the test group but this difference was not shown to be significant with the number of animals tested. A larger group encompassing a wider variety of individuals of different species would also allow assessment of novel hypotheses based on limited results from this study, including a higher incidence of post-operative nausea in macaws and a more profound sedative effect of butorphanol and midazolam in cockatoos.

References

1. Abou-Madi N (2001) Avian anesthesia. Vet Clin North Am, Exot Anim Pract 4:147-167, 2001

2. Acierno M, De Cunha A, Smith J et al. (2008) Measuring the level of agreement between indirect and direct blood pressure monitoring techniques in Hispaniolan Amazon parrots, J Am Vet Med Assoc 233, 1587–1590.

3. 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(3):199–204

4. 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 Xylazine, Ketamine, and Isoflurane for Induction and Maintenance of Anesthesia in Ostriches (*Struthio camelus*), Journal of Avian Medicine and Surgery 23(2):101–107, 2009

5. Bennett RA, (2008) Avian Anesthesia, Practitioners Symposium, ABVP 2008, Savannah GA, May 2-4

6. Biermann K, Hungerbühler S, Mischke R, Kästner SB. (2012), Sedative, cardiovascular, haematologic and biochemical effects of four different drug combinations administered intramuscularly in cats, Vet Anaesth Analg. 2012 Mar;39(2):137-50

7. Bigham AS, Zamani Moghaddam AK (1999), Finch (*Taeneopygia guttata*) sedation with intranasal administration of diazepam, midazolam or xylazine, J. vet. Pharmacol. Therap. 36, 102–104

8. Clyde VL, Paul-Murphy J (1999), Avian analgesia, in Fowler ME, Miller RE (eds): Zoo and Wild Animal Medicine: Current Therapy 4. Philadelphia, WB Saunders 1999, pp309-314

9. Concannon KT, Dodam JR, Hellyer PW(1995). Influence of a mu- and kappa-opioid agonist on isoflurane minimal anesthetic concentration in chickens. Am J Vet Res 1995;56:806-811

10. Curro TG (1994a), Evaluation of the isoflurane-sparing effects of butorphanol and flunixin in psittaciformes. Proc AAV Conf 1994; 17-19

11. Curro TG, Brunson DB, Paul-Murphy J (1994b), Determination of the ED50 of Isoflurane and evaluation of the isoflurane-sparing effect of butorphanol in cockatoos (*Cacatua* spp), Vet Surg 1994;23:429-433

12. Day TK, Roge CK (1996) Evaluation of sedation in quail induced by use of midazolam and reversed by use of flumazenil. J Am Vet Med Assoc 209, 969–971.

13. Dohoo SE (1990): Isoflurane as an inhalational anesthetic agent in clinical practice. Can Vet J 31:847-850, 1990

14. Doneley B, (2006) Pigeon medicine and surgery, Proceedings of the North American Veterinary Conference, Avian Medicine, 2006 pp 1-8

15. Dyson DH, (2008) Perioperative pain management in veterinary patients, Vet Clin Small Anim 38 (2008); 1309-1327

16. Dzikitia TB, Stegmanna GF, Hellebrekersb LJ, Auerc REJ, Dzikitid LN (2009), Sedative and cardiopulmonary effects of acepromazine, midazolam, butorphanol, acepromazine-butorphanol and midazolam-butorphanol on propofol anaesthesia in goats, Tydskr.S.Afr.vet.Ver. (2009) 80(1): 10–16

17. Edling IM, (2005) Anaesthesia and analgesia in Bsava manual of psittacines 2nd edition, eds Harcourt-Brown N, Chitty J, BSAVA publishing 2005 pp87-96

18. Edling TM (2006) Anesthesia and Monitoring. In: Harrison GJ, Lightfoot TL (eds) Clinical Avian Medicine Volume 1. Palm Beach, Fl, Spix Publishing, Inc, 2006, 747-760

19. Forbes NA, (1999) Birds, in BSAVA Manual of Small Animal Anaesthesia and Analgesia, eds Seymour C, Gleed R, BSAVA 1999

20. Gross ME, Smith JA, Tranquilli WJ. (1993), Cardiorespiratory effects of combined midazolam and butorphanol in isoflurane-anesthetized cats, Vet Surg. 1993 Mar-Apr;22(2):159-62.

21. Gunkel C, Lafortune M, (2005), Current Techniques in Avian Anesthesia, Seminars in Avian and Exotic Pet Medicine, Vol 14, No 4 (October), 2005: pp 263–276

22. Hawkins MG, Wright BD, Pascoe PJ, Kass PH, Maxwell LK, Tell LA (2003), Pharmacokinetics and anesthetic and cardiopulmonary effects of propofol in red-tailed hawks (*Buteo jamaicensis*) and great horned owls (*Bubo virginianus*), AJVR, Vol 64, No. 6, June 2003

23. Hawkins MG, Machin KL (2004), Avian pain and analgesia, Proc Assoc Avian Vet, New Orleans, LA, pp165-174, 2004

24. Hernandez-Divers, SJ, (2007) Avian Anesthesia, Atlantic Coast Veterinary Conference, Athens 2007

25. Hess L, (2002) Corticosteroid Synthesis and Metabolism in Birds, Seminars in Avian and Exotic Pet Medicine, Vol 11, No 2 (April), 2002: pp 65-70

26. Hildreth CD (2011) Feathers vs Fur–Cardiopulmonary Considerations for Avian Anesthesia, AAV 2011 Proceedings

27. Hofmeister EH, Mackey EB, Trim CM, (2008) Effect of butorphanol in isoflurane-anesthetized horses, Veterinary Anaesthesia and Analgesia, 2008, 35, 38–44

28. Hoppes S, Flammer K, Hoersch K, Papich M, Paul-Murphy J (2003), Disposition and analgesic effects of fentanyl in White cockatoos (*Cacatua alba*), J Avian Med Surg. September 2003;17(3):124-130

29. Ilkiw JE, Suter CM, Farver TB et al. (1996) The behaviour of healthy awake cats following intravenous and intramuscular administration of midazolam. J Vet Pharmacol Ther 19, 205–216.

30. Kay-Mugford P, Benn SJ, LaMArre J, Conlon P (2010), In vivo effects of nonsteroidal anti-inflammatory drugs on cyclooxygenase activity in dogs. Am J Vet Res 61(7):802-810, 2000

31. Kaufman GE, Paul Murphy JRP, Finnegan M, (1993). Preliminary evaluation of the effects of dexamethasone on serum hepatic enzymes, glucose, and total protein in Red-tailed Hawks, in Redig PT, Cooper JE, Remple ND, et al (eds): Raptor Biomcdicine. Minneapolis, MN, University of Minnesota Press, 1993, pp 184-187

32. Kirchgessner MS (2006), Meloxicam, Therapeutic review, Journal of Exotic Pet Medicine, Vol 15, No 4 (October), 2006: pp 281-283

33. Klaphake E, Schumacher J, Greenacre C, Jones MP, Zagaya N, (2006), Comparative Anesthetic and Cardiopulmonary Effects of Pre- Versus Postoperative Butorphanol Administration in Hispaniolan Amazon Parrots (*Amazona ventralis*) Anesthetized With Sevoflurane, Journal of Avian Medicine and Surgery 20(1):2–7, 2006

34. Kojima K, Nishimura R, Mutoh T, Takao K, Matsunaga S, Mochizuki M, Sasaki N, (1999a), Comparison of sedative effects of medetomidine-midazolam, acepromazine-butorphanol and midazolam-butorphanol in dogs, Zentralbl Veterinarmed A. 1999 Apr;46(3):141-8.

35. Kojima K, Nishimura R, Mutoh T, Takao K, Matsunaga S, Mochizuki M, Sasaki N (1999b), Comparison of cardiopulmonary effects of medetomidine-midazolam, acepromazine-butorphanol and midazolam-butorphanol in dogs, Zentralbl Veterinarmed A. 1999 Aug;46(6):353-9.

36. Lennox AM, (2011), Sedation as an Alternative to General Anesthesia in Pet Birds, AAV proceedings 2011

37. Ludders JW, Matthews N (1996) Anesthesia and immobilization of birds. In: Lumb and Jones' Veterinary Anesthesia (3rd edn). Thumon JC, Tranquilli WJ, Benson GJ (eds). William & Wilkins, Baltimore, MD, pp. 645–669.

38. Lukasik VM, (1999) Premedication and sedation, BSAVA Manual of Small Animal Anaesthesia and Analgesia, eds Seymour C, Gleed R, BSAVA 1999

39. LumeijJT (1999), Endocrinology, in: Ritchie BW, Harrison GJ, Harrison LR (eds): Avian Medicine: Principles and Application. Lake Worth, FL, Wingers Publishing, 1994, pp 599-601,

40. Machin KL, (2005) Controlling Avian Pain, Compendium on continuing education for the practicing veterinarian. Apr., v. 27, no. 4

41. Mans C, Sanchez-Migallon Guzman S, Lahner LL, Paul-Murphy JR, Sladky KK, (2011), Intranasal Midazolam Causes Conscious Sedation in Hispaniolan Amazon Parrots (*Amazona ventralis*), 2011 Proceedings AAV

42. Mansour A, Khachaturian H, Lewis ME, (1988) Anatomy of CNS opioid receptors, Trends Neurosc 1988; 11:308-314

43. McGeown D, Danbury TC, Waterman-Pearson AE, Kestin SC, (1999) Effect of carprofen on lameness in broiler chickens, The Veterinary Record,144; June 12, 1999, pp 668-671

44. Mutoh T, Nishimura R, Sasaki N,(2002) Effects of medetomidine-midazolam, midazolambutorphanol, or acepromazine-butorphanol as premedicants for mask induction of anesthesia with sevoflurane in dogs, American Journal of Veterinary Research, July 2002, Vol. 63, No. 7, Pages 1022-1028

45. Naidoo V, Wolter K, Cromarty AD, Bartels P, Bekker L, McGaw L, Taggart MA, Cuthbert R, Swan GE (2008). The pharmacokinetics of meloxicam in vultures, J Vet Pharmacol Ther. 2008 Apr;31(2):128-34

46. Nevarez JG (2005), Monitoring during avian and exotic pet anesthesia, Seminars in avian and exotic pet medicine, vol 14; no 4 (October), 2005: pp 277-283

47. Paul-Murphy J, Brunson DB, Miletic V (1999), Analgesic effects of butorphanol and buprenorphine in conscious African grey parrots (*Psittacus erithacus erithacus* and *Psittacus erithacus timneh*), Am J Vet Res 1999;60:1218-1221

48. Paul-Murphy J, Hess J, Fialkowski JP, (2004) Pharmokinetic properties of a single intra-muscular dose of buprenorphine in African grey parrots (*Psittacus erithacus erithacus*). J Avian Med Surg 2004; 18:224-228

49. Paul-Murphy J (2006), Pain Management, Chapter 8 in In: Harrison GJ, Lightfoot TL (eds) Clinical Avian Medicine Volume 1. Palm Beach, Fl, Spix Publishing, Inc, 2006 pp233-139

50. Pavez JC, Pascoe PJ, DiMaio Kynch HK (2010), Effect of fentanyl target-controlled infusions on Isoflurane MAD for red-tailed hawks (*Buteo jamaicensis*) Pric AAV Conf 2010;29

51. Pereira M, Werther K, (2004), Comparative evaluation of the renal effects of a seven-day therapy with flunixin meglumine, ketoprofen and meloxicam in budgerigar (*Melopsittacus undutatus*), Proc Annu Conf AAZV, AAWV, WDA 610-612, 2004

52. Plumb DC, (2002), Butorphanol tartrate in Plumb DC (ed), Veterinary Drug Handbook (4th ed). Ames IA, Iowa State Press, 2002, pp116-119

53. Reid J, Noal AM, (1999), Intravenous anaesthetics, in BSAVA Manual of Small Animal Anaesthesia and Analgesia, eds Seymour C, Gleed R, BSAVA 1999

54. Riggs SM, Hawkins MG, Craigmill AL, Kass PH, Stanley SD, Taylor IT (2008), Pharmacokinetics of butorphanol tartrate in red-tailed hawks (*Buteo jamaicensis*) and great horned owls (*Bubo virginianus*), AJVR, Vol 69, No. 5, May 2008

55. Sandmeier, P, (2000), Evaluation of Medetomidine for Short-Term Immobilization of Domestic Pigeons (*Columba livia*) and Amazon Parrots (*Amazona* species), Journal of Avian Medicine and Surgery 14(1):8–14, 2000

56. Schmidt PM, Gobel T, Trautvetter E, (1998) Evaluation of pulse oximetry as a monitoring method in avian anesthesia, JAMS 1998;12(2):91-98

57. Schroeder CA, Smith LJ, (2011), Respiratory Rates and Arterial Blood-Gas Tensions in Healthy Rabbits Given Buprenorphine, Butorphanol, Midazolam, or Their Combinations, Journal of the American Association for Laboratory Animal Science, Vol 50, No 2, March 2011, Pages 205–211

58. Short, C. E., Tyner, C. L., Matthews, N, McMurphy, R. (1987) Preanesthetic and postoperative pain relief in dogs: comparing analgesics. Veterinary Medicine 82, 744-751,

59. Sinha C, Kaur M, Kumar A, Kulkarni A, Ambareesha M, Upadya M, (2012), Comparative evaluation of midazolam and butorphanol as oral premedication in pediatric patients, J Anaesthesiol Clin Pharmacol 2012 Jan-Mar; 28(1):32-35

60. Sinn LC. (1994), Anesthesiology. In: Ritchie BW, Harrison GJ, Harrison LR, eds. Avian Medicine: Principles and Application. Lake Worth, FL: Wingers Publishing; 1994:1066–1080.

61. Sladky KK, Krugner-Higby L, Meek-Waler E (2006), Serum concentrations and analgesic effects of liposome-encapsulated and standard butorphanol tartrate in parrots. Am J Vet Res 2006;67:775-781

62. Smith J, Muir WW (1992) Cardiopulmonary effects of midazolam and flumazenil in racing pigeons. Vet Surg 21, 499.

63. Stick JA, Loeffler BS, Arden WA (1989) Effects of butorphanol tartrate on arterial pressure, jejunal blood flow, vascular resistance, O2 extraction, and O2 uptake in halothane-anesthetized ponies. Am J Vet Res 50, 1202–1206.

64. Valverde A, Honeyman VL, Smith DA et al. (1990) Determination of a sedative dose and influence of midazolam on cardiopulmonary function in Canada geese. Am J Vet Res 51, 1071–1074.

65. Vesal N, Zare P, (2006), Clinical evaluation of intranasal benzodiazepines, 2-agonists and their antagonists in canaries, Veterinary Anaesthesia and Analgesia, 2006, 33, 143–148

66. Vessal N, Eskandari MH, (2006), Sedative effects of midazolam and xylazine with or without ketamine and detomidine alone following intranasal administration in Ring-necked Parakeets, JAVMA, Vol 228, No. 3, February 1, 2006

67. Wilson GH, Hernandez-Divers S, Budsberg SC, Latimer KS, Grant K, Pethel M, (2004), Pharmacokinetics and Use of Meloxicam in Psittacine Birds, AAV Proceedings (210), 2004

68. Wilson JE, Chandrasekharan NV, Westover KD, Eager KB, Simmons DL, (2004), Determination of expression of cyclooxygenase 1 and 2 isoenzymes in canine tissue and their differential sensitivity to nonsteroidal anti-inflammatory drugs. Am J Vet Res 65(6):810-818, 2004

69. Wright EM, Marcella KL, Woodson JF, (1985), Animal pain and control. Lab Anim May/June:20-36, 1985

70. Zamani Moghadam AK, Sadegh AB, Sharif S, Habibian S, (2009), Comparison of intranasal administration of diazepam, midazolam and xylazine in Pigeons: Clinical evaluation, Iranian Journal of Veterinary Science and Technology Vol. 1, No. 1, Summer 2009, 19-26

71. Zehnder AM, Hawkins MG, Pascoe PJ, Kass PH,(2009) Veterinary Anaesthesia and Analgesia, 2009, 36, 464–479Evaluation of indirect blood pressure monitoring in awake and anesthetized red-tailed hawks (*Buteo jamaicensis*): effects of cuff size, cuff placement, and monitoring equipment, Veterinary Anaesthesia and Analgesia, 2009, 36, 464–479

72. Zhang Y, Eger II EI, Dutton RC, (2000), Inhaled anesthetics have hyperalgesic effects at 0.1 minimum alveolar anesthetic concentration. Anesth Analg 91: 462-466, 2000

	NP1	NP2	NP3	NP4	NP5	NP6	NP7	NP8	NP9	**Mean values**
Interval between injection and induction (mins)	15.00	15.00	15.00	23.00	15.00	15.00	15.00	15.00	15.00	**15.89**
Time from induction to intubation (s)	69.00	130.00	90.00	80.00	150.00	100.00	131.00	83.00	49.00	**98.00**
Quality score of induction (mean value)	1.50	5.00	2.00	3.00	2.50	2.50	3.50	2.00	4.00	**2.89**
Duration of anaesthesia (mins)	13.00	14.00	13.00	5.00	12.00	18.00	5.00	8.00	7.00	**10.56**
Average isoflurane percentage	3.00	3.07	3.14	2.50	3.54	2.76	3.50	2.78	2.88	**3.02**
Average heart rate (per minute)	239.43	160.00	184.00	204.00	263.75	190.00	249.00	190.40	259.60	**215.58**
Average respiratory rate (per minute)	34.00	13.29	24.57	49.33	28.25	17.33	64.25	31.40	23.60	**31.78**
Presence of toe pinch	0, 2, 4 mins	None	0 mins	0 mins	0, 2 mins	0 mins	0 , 4mins	none	0 mins	**7 of 9**
Pulse oximetry (mean value) %	100.00	No value	99.83	97.67	No value	99.90	96.67	100.00	99.80	**99.12**
Temperature drop (C/min)	0.07	0.14	0.11	0.10	0.24	0.16	0.19	0.28	0.04	**0.15**
Blood pressure (mmHg)	210.00	No value	No value	No value	No value	167.50	270.00	140.00	210.00	**199.50**
Average end tidal CO2 (mmHg)	50.6	27.6	No value	No value	47.6	39.3	40.1	23.7	40.4	**38.5**
Peak ETCO2 (mmHg)	89.0	47.0	No value	No value	80.0	51.0	47.0	31.0	46.0	**55.86**
Time from Isoflurane off to extubation (s)	114.00	105.00	120.00	30.00	120.00	15.00	104.00	136.00	117.00	**95.67**
Quality score of recovery (mean value)	1.00	2.50	1.00	2.00	2.00	3.00	2.50	2.00	4.00	**2.22**
Time from extubation to perching (s)	638.00	220.00	540.00	115.00	280.00	282.00	116.00	303.00	61.00	**283.89**

Table 1. Anaesthetic monitoring parameters recorded for parrots administered saline prior to anaesthesia.

	P1	P2	P3	P4	P5	P6	P7	P8	**Mean values**
Interval between injection and induction (mins)	22.00	15.00	15.00	15.00	14.00	15.00	16.00	14.00	**15.75**
Time from induction to intubation (s)	105.00	45.00	60.00	34.00	40.00	59.00	66.00	110.00	**64.88**
Quality score of induction (mean value)	1.00	2.00	1.00	1.00	1.00	3.00	2.00	1.00	**1.50**
Duration of anaesthesia (mins)	8.00	7.00	12.00	18.00	9.00	10.00	8.00	10.00	**10.25**
Average isoflurane percentage	3.44	2.63	2.85	2.26	1.10	1.82	2.50	1.64	**2.28**
Average heart rate (per minute)	155.00	173.00	287.33	226.67	191.00	193.33	284.40	286.33	**224.63**
Average respiratory rate (Per minute)	20.60	40.67	28.75	30.33	23.17	10.00	32.80	18.33	**25.58**
Presence of toe pinch	None	None	2mins	None	None	None	None	0 mins	**2 of 8**
Pulse oximetry (mean value) %	No value	100.00	98.00	99.25	93.75	99.50	95.00	99.67	**97.88**
Temperature drop (C/min)	0.20	0.10	0.19	0.19	0.07	0.10	0.23	0.06	**0.14**
Blood pressure (mmHg)	No value	260.00	182.50	125.00	248.00	133.33	90.00	105.00	**163.40**
Average end tidal CO2 (mmHg)	24.00	57.00	44.10	31.20	37.10	39.10	40.50	29.10	**37.76**
Peak ETCO2 (mmHg)	24.00	87.00	88.00	65.00	40.00	70.00	62.00	43.0	**59.88**
Time from Isoflurane off to extubation (s)	180.00	193.00	252.00	181.00	81.00	37.00	103.00	126.00	**144.13**
Quality score of recovery (mean value)	2.00	2.00	4.00	1.50	1.50	4.00	2.50	2.00	**2.44**
Time from extubation to perching (s)	480.00	215.00	1254.00	745.00	604.00	421.00	227.00	167.00	**514.13**

Table 2. Anaesthetic monitoring parameters recorded for parrots administered a butorphanol and midazolam pre-medicant combination prior to anaesthesia.

	AGP	AGP	AGP	AGP	AGP	
	NP1	NP3	NP4	NP5	NP7	**Mean values**
Interval between injection and induction (mins)	15.00	15.00	23.00	15.00	15	**16.60**
Time from induction to intubation (s)	69.00	90.00	80.00	150.00	131	**104.00**
Quality score of induction (mean value)	1.50	2.00	3.00	2.50	3.5	**2.50**
Duration of anaesthesia (mins)	13.00	13.00	5.00	12.00	5	**9.60**
Average isoflurane percentage	3.00	3.14	2.50	3.54	3.5	**3.14**
Average heart rate (per minute)	239.43	184.00	204.00	263.75	249	**228.04**
Average respiratory rate (per minute)	34.00	24.57	49.33	28.25	64.25	**40.08**
Presence of toe pinch	0, 2, 4 mins	0 mins	0 mins	0, 2 mins	0, 4mins	**5 of 5**
Pulse oximetry (mean value) %	100.00	99.83	97.67	No value	96.67	**98.54**
Temperature drop (C/min)	0.07	0.11	0.10	0.24	0.19	**0.14**
Blood pressure (mmHg)	210.00	No value	No value	No value	270	**240.00**
Average end tidal CO2 (mmHg)	50.6	No value	No value	47.6	40.1	**46.1**
Peak ETCO2 (mmHg)	89.0	No value	No value	80.0	47.0	**72.0**
Time from Isoflurane off to extubation (s)	114.00	120.00	30.00	120.00	104	**97.60**
Quality score of recovery (mean value)	1.00	1.00	2.00	2.00	2.5	**1.70**
Time from extubation to perching (s)	638.00	540.00	115.00	280.00	116	**337.80**

Table 3, Anaesthetic monitoring parameters recorded for old world parrots administered saline prior to anaesthesia. (AGP = African Grey (*Psittacus erithacus*))

	AGP	AGP	AGP	cockatoo		
	P2	P3	P4	P5	**Mean values**	**Mean AGP values**
Interval between injection and induction (mins)	15.00	15.00	15.00	14.00	**14.75**	**15.00**
Time from induction to intubation (s)	45.00	60.00	34.00	40.00	**44.75**	**46.33**
Quality score of induction (mean value)	2.00	1.00	1.00	1.00	**1.25**	**1.33**
Duration of anaesthesia (mins)	7.00	12.00	18.00	9.00	**11.50**	**12.33**
Average isoflurane percentage	2.63	2.85	2.26	1.10	**2.21**	**2.58**
Average heart rate (per minute)	173.00	287.33	226.67	191.00	**219.50**	**229.00**
Average respiratory rate (per minute)	40.67	28.75	30.33	23.17	**30.73**	**33.25**
Presence of toe pinch	None	2mins	None	None	**1 of 4**	**1 of 3**
Pulse oximetry (mean value) %	100.00	98.00	99.25	93.75	**97.75**	**99.08**
Temperature drop (C/min)	0.10	0.19	0.19	0.07	**0.14**	**0.16**
Blood pressure (mmHg)	260.00	182.50	125.00	248.00	**203.88**	**189.17**
Average end tidal CO2 (mmHg)	57.0	44.1	31.2	37.1	**42.4**	**44.1**
Peak ETCO2 (mmHg)	87.0	88.0	65.0	40.0	**70.0**	**80.0**
Time from Isoflurane off to extubation (s)	193.00	252.00	181.00	81.00	**176.75**	**208.67**
Quality score of recovery (mean value)	2.00	4.00	1.50	1.50	**2.25**	**2.50**
Time from extubation to perching (s)	215.00	1254.00	745.00	604.00	**704.50**	**738.00**

Table 4. Anaesthetic monitoring parameters recorded for old world parrots administered a butorphanol and midazolam pre-medicant combination prior to anaesthesia. (AGP = African Grey (*Psittacus erithacus*), cockatoo= Umbrella cockatoo (*Cacatua alba*))

	B&G	YHA	Hahns	OWA	
	NP2	NP6	NP8	NP9	**Mean values**
Interval between injection and induction (mins)	15.00	15.00	15.00	15.00	**15.00**
Time from induction to intubation (s)	130.00	100.00	83.00	49.00	**90.50**
Quality score of induction (mean value)	5.00	2.50	2.00	4.00	**3.38**
Duration of anaesthesia (mins)	14.00	18.00	8.00	7.00	**11.75**
Average isoflurane percentage	3.07	2.76	2.78	2.88	**2.87**
Average heart rate (per minute)	160.00	190.00	190.40	259.60	**200.00**
Average respiratory rate (per minute)	13.29	17.33	31.40	23.60	**21.40**
Presence of toe pinch	None	0 mins	none	0 mins	**1 of 4**
Pulse oximetry (mean value) %	No value	99.90	100.00	99.80	**99.90**
Temperature drop (C/min)	0.14	0.16	0.28	0.04	**0.16**
Blood pressure (mmHg)	No value	167.50	140.00	210.00	**172.50**
Average end tidal CO2 (mmHg)	27.60	39.30	23.70	40.40	**32.75**
Peak ETCO2 (mmHg)	47.00	51.00	31.00	46.00	**43.75**
Time from Isoflurane off to extubation (s)	105.00	15.00	136.00	117.00	**93.25**
Quality score of recovery (mean value)	2.50	3.00	2.00	4.00	**2.88**
Time from extubation to perching (s)	220.00	282.00	303.00	61.00	**216.50**

Table 5, Anaesthetic monitoring parameters recorded for new world parrots administered saline prior to anaesthesia. (B&G= Blue and Gold Macaw (*Ara Arauana*), YHA = Double yellow headed amazon (*Amazona oratrix*), Hahns = Hahn's Macaw (*Diopsittaca nobilis)*, OWA= Orange winged amazon (*Amazona amazonica*))

	B&G	B&G	Hahns	OWA	
	P1	P6	P7	P8	**Mean values**
Interval between injection and induction (mins)	22.00	15.00	16.00	14.00	**16.75**
Time from induction to intubation (s)	105.00	59.00	66.00	110.00	**85.00**
Quality score of induction (mean value)	1.00	3.00	2.00	1.00	**1.75**
Duration of anaesthesia (mins)	8.00	10.00	8.00	10.00	**9.00**
Average isoflurane percentage	3.44	1.82	2.50	1.64	**2.35**
Average heart rate (per minute)	155.00	193.33	284.40	286.33	**229.77**
Average respiratory rate (per minute)	20.60	10.00	32.80	18.33	**20.43**
Presence of toe pinch	None	None	None	0 mins	**1 of 4**
Pulse oximetry (mean value) %	No value	99.50	95.00	99.67	**98.06**
Temperature drop (C/min)	0.20	0.10	0.23	0.06	**0.15**
Blood pressure (mmHg)	No value	133.33	90.00	105.00	**109.44**
Average end tidal CO2 (mmHg)	24.00	39.10	40.50	29.10	**33.18**
Peak ETCO2 (mmHg)	24.00	70.00	62.00	43.00	**49.75**
Time from Isoflurane off to extubation (s)	180.00	37.00	103.00	126.00	**111.50**
Quality score of recovery (mean value)	2.00	4.00	2.50	2.00	**2.63**
Time from extubation to perching (s)	480.00	421.00	227.00	167.00	**323.75**

Table 6. Anaesthetic monitoring parameters recorded for new world parrots administered a butorphanol and midazolam pre-medicant combination prior to anaesthesia. (B&G= Blue and Gold Macaw (*Ara Arauana*), Hahns = Hahn's Macaw (*Diopsittaca nobilis)*, OWA= Orange winged amazon (*Amazona amazonica*))

Appendix 1: Data recording sheet

Patient no.		Nurse
Species		Observer 1
Age		Observer 2
Sex:	Male/female/unknown	
Procedure		

Pre-med: Yes ☐ No ☐ **To complete after procedure**

Time of injection …… Time of induction ……

Time from induction to intubation ……

Quality of induction

1. No struggling/avoidance behaviour ☐
2. Minor avoidance behaviour (random head and body movements), no vocalisation ☐
3. Purposeful attempts to move away from mask ☐
4. Repeated escape attempts and vocalisation ☐
5. Bird difficult to restrain, wing flapping, struggling and vocalisation ☐

Time (mins	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Iso %																					
ETCO2																					
Heart rate																					
Respiratory rate																					
Toe pinch present?																					
Pulse ox																					
Temperature																					
Blood pressure																					

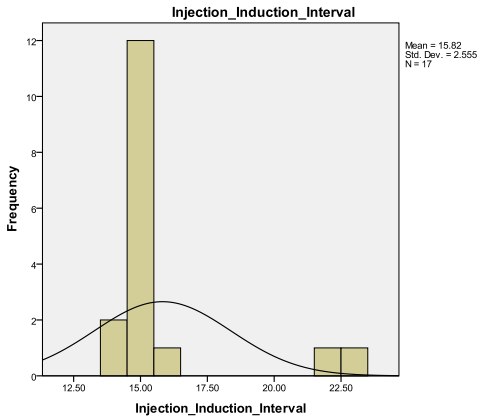
Time from Isoflurane off to extubation ……

Quality of recovery

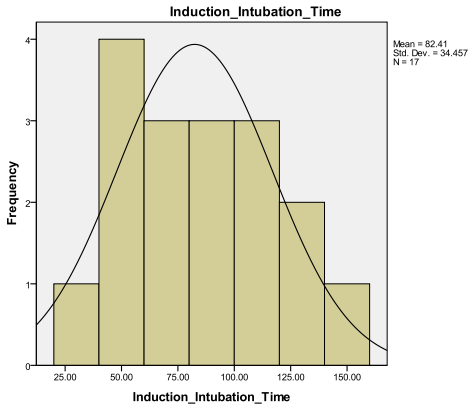
1. No excitement ☐
2. Mild excitement with poorly co-ordinated movements ☐
3. Struggling and vocalisation ☐
4. Short periods of rolling and wing flapping ☐
5. Continuous flapping, rolling and vocalisation ☐

Time from extubation to perching …….

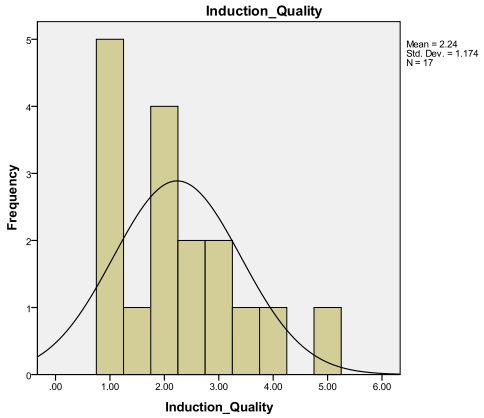
Appendix 2: Histogram Depiction of Data



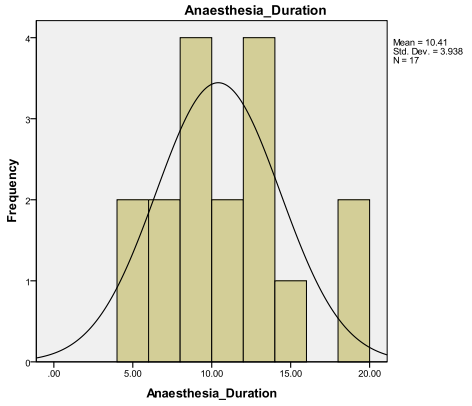
Parameter not under statistical analysis



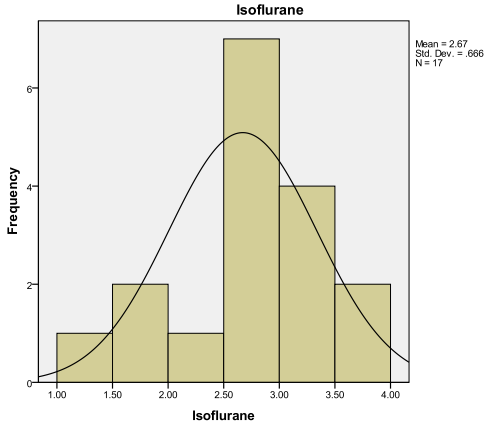
Conclusion: Normal distribution, parametric assessment



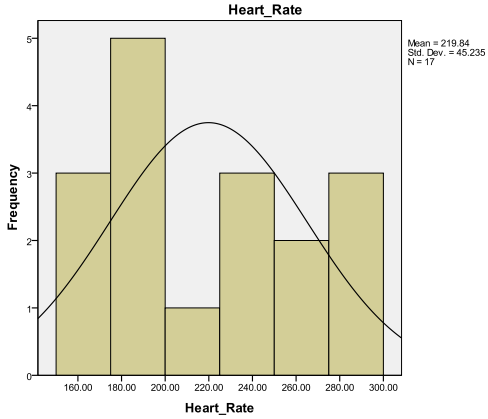
Quality measure: non-parametric assessment



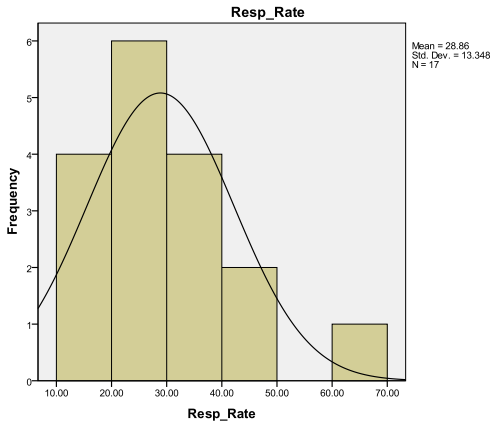
Parameter not under statistical analysis



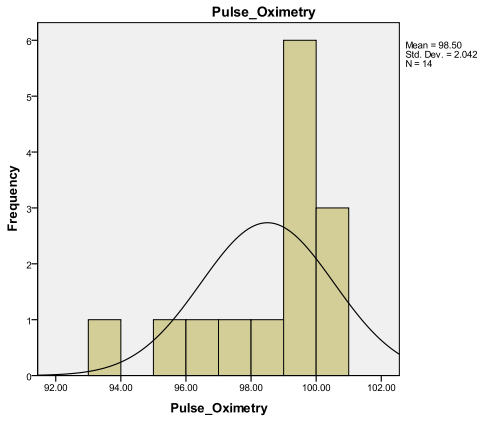
Conclusion: Normal distribution, parametric assessment



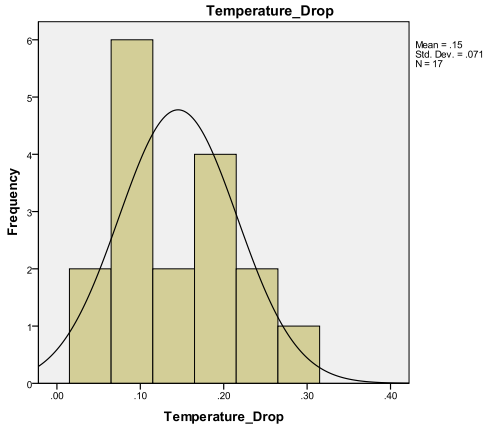
Conclusion: Not normal distribution, non-parametric assessment



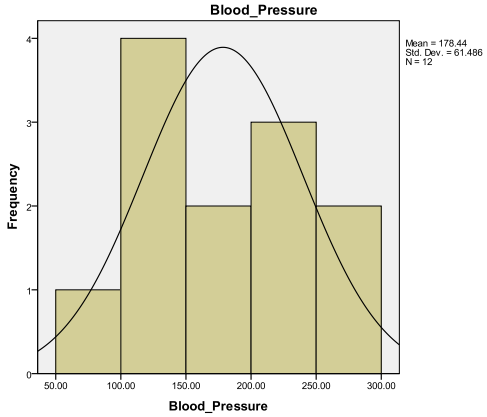
Conclusion: Normal distribution, parametric assessment



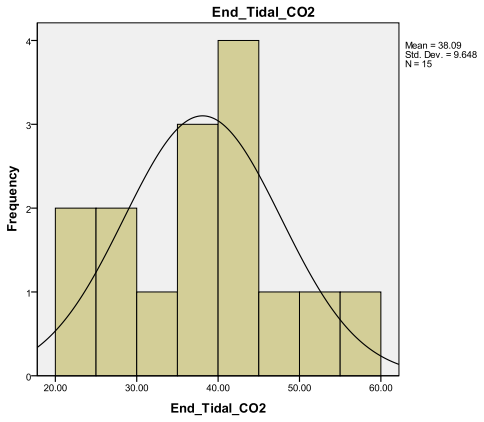
Conclusion: Not normal distribution, non-parametric assessment



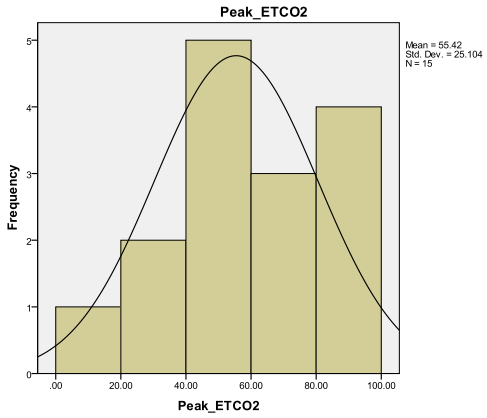
Conclusion: Normal distribution, parametric assessment



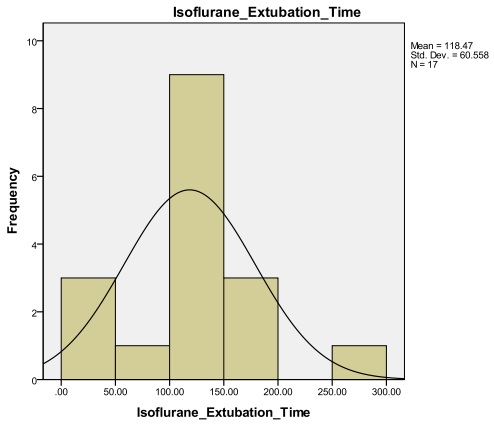
Conclusion: Normal distribution, parametric assessment



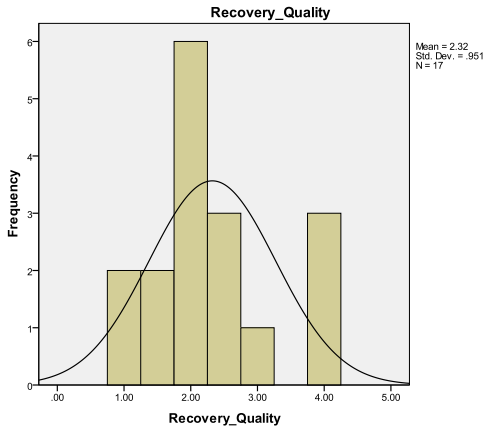
Conclusion: Normal distribution, parametric assessment



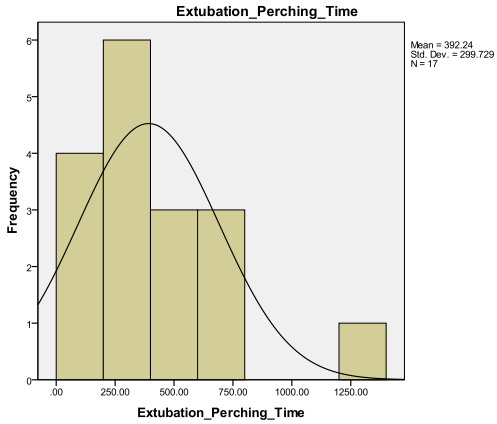
Conclusion: Normal distribution, parametric assessment



Conclusion: Normal distribution, parametric assessment



Quality measure: non-parametric assessment



Conclusion: Not normal distribution, non-parametric assessment

Appendix 3, Mean, Standard Deviation and Median Values

Mean, Standard Deviation and standard error mean values

Group Statistics

	Group	N	Mean	Std. Deviation	Std. Error Mean
Injection_Induction_Interval	Control	9	15.8889	2.66667	.88889
	Test	8	15.7500	2.60494	.92099
Induction_Intubation_Time	Control	9	98.0000	32.93175	10.97725
	Test	8	64.8750	28.46771	10.06486
Anaesthesia_Duration	Control	9	10.5556	4.50309	1.50103
	Test	8	10.2500	3.49489	1.23563
Isoflurane	Control	9	3.0189	.34156	.11385
	Test	8	2.2800	.74214	.26239
Heart_Rate	Control	9	215.5756	37.83637	12.61212
	Test	8	224.6325	54.69324	19.33698
Resp_Rate	Control	9	31.7800	16.00553	5.33518
	Test	8	25.5812	9.54953	3.37627
Pulse_Oximetry	Control	7	99.1243	1.36800	.51706
	Test	7	97.8814	2.50218	.94574
Temperature_Drop	Control	9	.1478	.07855	.02618
	Test	8	.1425	.06671	.02358
Blood_Pressure	Control	5	199.5000	49.38370	22.08506
	Test	7	163.4043	68.35010	25.83391
End_Tidal_CO2	Control	7	38.4714	9.77986	3.69644
	Test	8	37.7625	10.19439	3.60426
Peak_ETCO2	Control	7	55.8571	20.72381	7.83286
	Test	8	55.0375	29.86512	10.55892
Isoflurane_Extubation_Time	Control	9	95.6667	42.68782	14.22927
	Test	8	144.1250	69.84971	24.69560
Extubation_Perching_Time	Control	9	283.8889	194.24305	64.74768
	Test	8	514.1250	360.76207	127.54865

Calculated median value for each variable for control and test groups

	Injection_Induction_Interval	Induction_Intubation_Time	Induction_Quality	Anaesthesia_Duration	Isoflurane	Heart_Rate
Control	15.0000	90.0000	2.5000	12.0000	3.0000	204.0000
Test	15.0000	59.5000	1.0000	9.5000	2.3800	210.0000

	Resp_Rate	Pulse_Oximetry	Temperature_Drop	Blood_Pressure	End_Tidal_CO2	Peak_ETCO2
Control	28.2500	99.8300	.1400	210.0000	40.1000	47.0000
Test	25.9600	99.2500	.1450	133.3300	38.1000	63.5000

	Isoflurane_Extubation_Time	Recovery_Quality	Extubation_Perching_Time
Control	114.0000	2.0000	280.0000
Test	153.0000	2.0000	450.5000

Appendix 4: Effect sizes

	Was t test significant?	T test effect size	Was MW significant?	Mann Whitney effect size
Injection_Induction_Interval	N		N	
Induction_Intubation_Time	Y	*r* = 0.49 small to medium	Y	*r* = 0.49 small to medium
Induction_Quality	N/A		Y	*r* = 0.63 large
Anaesthesia_Duration	N		N	
Isoflurane	Y	*r* = 0.57 large	Y	*r* = 0.57 large
Heart_Rate	N		N	
Resp_Rate	N		N	
Pulse_Oximetry	N		N	
Temperature_Drop	N		N	
Blood_Pressure	N		N	
End_Tidal_CO2	N		N	
Peak_ETCO2	N		N	
Isoflurane_Extubation_Time	N		N	
Recovery_Quality	N/A		N	
Extubation_Perching_Time	N		N	

r = 0.10 = small effect

r = 0.30 = medium effect

r = 0.50 = large effect