**Effects of atipamezole dosage and timing of administration on recovery time and quality in cats following injectable anaesthesia incorporating ketamine**

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**Abstract**

**Objectives** To establish the optimum dosage and timing of administration of atipamezole in cats undergoing general anaesthesia incorporating ketamine to provide the shortest recovery possible without unacceptably compromising recovery quality.

**Methods** One hundred and twenty eight healthy male cats (age range 2–108 months, weight range 0.56–5.22 kg) admitted for castration were randomly allocated to groups of 32. Anaesthesia was induced with 60 mg/m2 ketamine, 180 µg/m2 buprenorphine, 3mg/m2 midazolam and 600 µg/m2 medetomidine intramuscularly (IM). Cats received 600 μg/m2 (groups 1ATI20 and 1ATI40) or 1.5 mg/m2 (groups 2.5ATI20 and 2.5ATI40) atipamezole IM either 20 (groups 1ATI20 and 2.5ATI20) or 40 mins (groups 1ATI40 and 2.5ATI40) after the 'quad'. Preparation time, surgical time, auricular temperature, times to sternal recumbency and first standing and recovery quality score were recorded. Data were analysed using ANOVA, Kruskal-Wallis, Mann-Whitney U-tests and χ2 tests. Statistical significance was deemed to be *P*≤0.05.

**Results** Groups did not differ significantly in preparation or surgical time. Auricular temperature decreased significantly over time (P<0.01) but did not differ between atipamezole treatment groups. Time to sternal recumbency in group 2.5ATI20 (52.9 ± 22.3 mins) was faster than group 1ATI20 (65.7 ± 24.7 mins) (P≤0.05) but there were no significant differences between other groups. Time to first standing and recovery quality scores did not differ significantly between groups. Minimal adverse effects were seen.

**Conclusions and relevance** Atipamezole administration after 20 mins did not reduce recovery time but neither was recovery quality adversely affected compared to when administered after 40 mins following datasheet recommendations with concurrent ketamine administration. The results of this study also suggest that an atipamezole:medetomidine dose ratio of 2.5:1 is more effective than 1:1 in reducing recovery time regardless of timing of administration, although this only reached statistical significance for time to sternal recumbency when atipamezole was administered after 20 mins.

**Introduction**

Gonadectomy is routinely performed in cats in the UK to prevent unwanted litters and improve cat population control.1,2 Prepubertal gonadectomy in male cats has been shown to reduce the occurrence of undesirable behaviours such as aggression, sexual behaviours and urine spraying compared to cats that underwent postpubertal gonadectomy.3 The Royal Society for the Prevention of Cruelty to Animals (RSPCA) and other animal charities are involved in cat neutering programs for public owned cats, shelter cats prior to re-homing and feral cats in an attempt to control cat overpopulation in the UK. The RSPCA Greater Manchester Animal Hospital (GMAH) alone currently performs approximately 600 cat castrations per annum (D Yates, unpublished data).

Injectable anaesthetic protocols combining α2-adrenoceptor agonists and ketamine are commonly used for domestic and feral cat neutering.1,4-8 Anaesthetic protocols that result in shorter recovery times are likely to be beneficial in reducing the risks of post-anaesthetic hypothermia9 and mortality.10 Shorter recoveries would also enable earlier discharge from the hospital which is potentially beneficial to cats in terms of stress reduction and reduced risk of nosocomial infection and also beneficial to hospital management in terms of reducing staff time in monitoring recoveries in addition to allowing a higher intake of cats for neutering.4

Atipamezole has consistently been shown to shorten recovery times when administered to cats that have received α2-adrenoceptor agonists.4,6,7 The current datasheet recommendation for atipamezole dosing in cats is an atipamezole:medetomidine dose ratio of 2.5:1.11 This follows recommendations from previous research in cats where this atipamezole dose effectively reversed sedation and bradycardia when administered 30 mins after medetomidine and ketamine whilst a dose ratio of 6.25:1 produced undesirable tachycardia.12 However, both experimental and clinical studies in cats have demonstrated variable efficacy of different atipamezole doses. One study concluded that an atipamezole:medetomidine dose ratio range of 2:1 to 4:1 was effective for antagonising medetomidine in clinical cases.13 However, a later study assessing sleep-wake cycles as well as sedation reversal following medetomidine and subsequent atipamezole administration to cats reported that a dose ratio of 2:1 was effective in reversing sedation but ratios of 4:1 or 8:1 were more effective in restoring sleep-wake cycles.14

Published literature evaluating atipamezole:medetomidine dose ratios lower than 2:1 is sparse. A dose ratio of 1:1 was used experimentally in healthy cats to assess the effects of different atipamezole doses on medetomidine-induced diuresis but the authors do not comment on the sedative effects or antagonism thereof for this dose.15 A recent paper assessed the haemodynamic effects of 'low dose' intravenous atipamezole following dexmedetomidine infusion in anaesthetised cats but all cats ultimately received an atipamezole:dexmedetomidine dose ratio of 5:1 so the effects of 'low dose' atipamezole on sedation reversal and recovery time were not assessed.16

Concerns regarding the adverse effects of ketamine on recovery quality due to its ability to induce dysphoria, excitation, ataxia and muscle hypertonus have previously been raised.12,17,18 Therefore, judicious timing of atipamezole administration has been advocated in cats that have received ketamine, with current datasheet recommendations suggesting that atipamezole should not be administered within 30–40 mins of prior ketamine administration.11

However, literature evidence for ketamine resulting in poor recoveries is contradictory. Recovery quality was deemed to be excellent following atipamezole administration to 31 out of 34 cats undergoing various surgical procedures that had received intramuscular medetomidine and ketamine.19 However, the recovery quality scoring system was not described, the timing of atipamezole administration was variable depending on procedure duration and some cats received two doses of atipamezole if adequate arousal was not observed within 15 mins of the first dose. Another study reported that all cats demonstrated moderate ataxia in recovery when atipamezole was administered 30 mins after medetomidine and ketamine and the authors attributed this to the presence of residual ketamine following medetomidine antagonism.12 Two studies comparing administration of ketamine or alfaxalone in combination with various anaesthetic drugs reported poorer recovery quality in cats that received ketamine compared to alfaxalone.17,18 However, another study using dexmedetomidine and ketamine with various opioids followed by atipamezole or saline placebo in cats undergoing castration found no differences in recovery quality despite administration of atipamezole as early as 13 mins after the initial anaesthetic drug combination.7

The purpose of this study was to attempt to establish the optimum dosage and timing of administration of atipamezole in cats undergoing a short general anaesthetic in order to provide the shortest recovery possible without unacceptably compromising recovery quality. The current datasheet recommendation to administer atipamezole 30-40 mins after ketamine could potentially result in a unnecessarily prolonged recovery time after short procedures. Therefore, the aims of this study were to firstly compare the effects of the licensed atipamezole dose (atipamezole:medetomidine dose ratio of 2.5:1) with a lower atipamezole dose (1:1) on recovery time and quality in cats after castration using an anaesthetic protocol incorporating ketamine and secondly to investigate the effects of earlier administration of both atipamezole doses on recovery time and quality compared to the datasheet recommendation. The authors hypothesised that there would be minimal differences in recovery time and quality between the two different doses of atipamezole but that earlier administration of atipamezole would result in shorter recoveries of poorer quality.

**Materials and methods**

This study was approved by the University of Liverpool Veterinary Research Ethics Committee (VREC540) and an Animal Test Certificate was obtained from the Veterinary Medicines Directorate (ATC-S-086). Written informed consent was obtained from all owners upon admission of study cats to the hospital and the RSPCA provided written informed consent for all stray cats that were participating in the study prior to re-homing.

One hundred and twenty eight entire male cats of any age or breed presented for castration at the RSPCA GMAH between June 2017 and January 2018 were included. Any prior clinical history was reviewed if available and physical examination was performed on all cats upon admission to ensure that they were healthy or not showing signs of systemic disease likely to affect the general anaesthetic (American Society of Anesthesiologists’ (ASA) classification I or II). Any sick cats (ASA classification ≥ III), female cats or cryptorchid males admitted for neutering between these dates were excluded from the study. Preoperative fasting for eight hours was advised with a maximum of four hours recommended for any cats ≤ 4 months old.

The anaesthetic protocol was based on the GMAH ‘quad’ anaesthetic protocol for prepubertal cat neutering which has been previously reported.1,4,20 Discussion and justification of the four drugs incorporated in the 'quad' protocol have been published previously.1,4 The 'quad' protocol was devised according to body surface area (BSA) as follows: 60 mg/m2 ketamine (Anesketin; Dechra), 180 μg/m2 buprenorphine (Buprenodale; Dechra), 3 mg/m2 midazolam (Hypnovel; Roche) and 600 μg/m2 medetomidine (Sedator; Dechra) which equates to equal volumes of each agent given in a single intramuscular (IM) injection to induce general anaesthesia. BSA was calculated as BSA = (K × BW2/3)/100, where BSA is measured in m2, body weight (BW) in kg and K = 10.4 for cats.1 As previously described, BSA was used for drug dose calculations instead of bodyweight in order to account for relative under-dosing of drugs in paediatric cats and to allow allometric scaling.1

Cats were randomly allocated into four groups of 32 based on order of hospital admission using www.randomizer.org/form.htm. Each group received the following treatments: group 1ATI20 - 'quad' followed by 600 μg/m2 atipamezole (Atipam; Dechra) IM 20 mins later (atipamezole:medetomidine dose ratio of 1:1 equating to 20% of medetomidine volume); group 2.5ATI20 - 'quad' followed by 1.5 mg/m2 atipamezole IM 20 mins later (atipamezole: medetomidine dose ratio of 2.5:1 equating to 50% of medetomidine volume); group 1ATI40 - 'quad' followed by 600 μg/m2 atipamezole 40 mins later; group 2.5ATI40 - 'quad' followed by 1.5 mg/m2 atipamezole IM 40 mins later as recommended on the atipamezole datasheet.11

The four drugs in the ‘quad’ were mixed into one syringe immediately before administration into the left quadriceps muscle. Surgery commenced as soon as anaesthetic depth was considered sufficient using normal clinical criteria. All cats additionally received 3 mg/m2 meloxicam (Metacam; Boehringer Ingelheim) subcutaneously (SC) prior to commencing surgery. Oxygen was supplemented via mask using an infant T-piece (Mapleson D) at 400 ml/kg/min throughout the procedure and surgery was performed on a preheated operating table set to 37ºC. Isoflurane was administered via a tight fitting mask if depth of anaesthesia was deemed insufficient.

Bilateral scrotal incisions were made and open castration was performed. Scrotal skin incisions were left to heal by secondary intention. The surgical procedure was very short (generally <4 mins) and anaesthetic monitoring was limited to observation of vital signs and thoracic auscultation with a stethoscope (mucous membrane colour, capillary refill time, respiratory rate, heart rate and adequacy of anaesthetic depth).

Body weight, ASA status and age of all cats were recorded as well as time of the ‘quad’ injection, preparation time (time from 'quad' injection to commencing surgery), total surgical time (from first scrotal incision to removal of second testis), time when first reaching sternal recumbency and time when first standing. Auricular temperature was measured using an Instant Ear Thermometer (Vet-Temp; Advanced Monitors Corporation) at four time points in each cat: immediately prior to commencing surgery (T1), at the end of surgery (T2), 20 mins after 'quad' injection (T3) and 40 mins after 'quad' injection (T4).

Recovery quality was also scored by one blinded, experienced veterinary nurse using a scale of 1-5 previously described in another feline study where 1 = poor (many attempts to stand, frequent falling over and marked ataxia), 2 = better (multiple attempts to stand, occasionally falling and significant ataxia), 3 = good (cat lying quietly before taking several attempts to stand with some ataxia), 4 = very good (only a few attempts to stand and mild ataxia) and 5 = excellent (cat rolls into sternal recumbency and stands with minimal ataxia and without falling).21 Any other significant events such as requirement for isoflurane and any adverse events noted during the procedure or recovery period e.g. haemorrhage, vomiting or dysphoria were also recorded.

Artificial tears (Lubrithal; Dechra) were applied to the eyes of all cats prior to commencing surgery to provide corneal lubrication. All cats were placed in individual kennels preheated to 37ºC for recovery; once in sternal recumbency the temperature was reduced to 25ºC. Food was offered as soon as cats were reliably standing and a recovery quality score had been assigned.

One veterinary surgeon prepared and administered drugs (NB) and two surgeons (KH and AE) performed all the surgeries throughout the study. Anaesthetic monitoring was performed by one trainee veterinary nurse (JH) under the direct supervision of the anaesthetist (NB). Recovery was monitored and recorded by the same experienced veterinary nurse (AH) throughout the study. The anaesthetist (NB) performed all of the auricular temperature measurements. The nurse monitoring the recoveries and operating surgeons were blinded to the treatment groups.

Data are described as mean (± SD) for normally distributed data and median [inter-quartile range (IQR)] for non-parametric data unless stated otherwise. Statistical analyses were performed using IBM SPSS Statistics version 25 for Windows. Kolmogorov-Smirnov and Shapiro-Wilk tests were performed in addition to visual inspection of histograms to assess for normality. Logarithmic transformations of time to sternal recumbency and time to first standing data were performed to facilitate the assumptions of ANOVA under parametric conditions. One way ANOVA and post-hoc Tukey's test were used to compare normally distributed data between groups (preparation time, T1-T4 temperature data, log10 time to sternal recumbency and log10 time to first standing). One way repeated measures ANOVA with Bonferroni adjustments were used to compare temperature data at the four time points within treatment groups. Kruskal-Wallis with Mann-Whitney U-test pairwise comparisons and Bonferroni adjustments were performed to compare non-parametric data between treatment groups. Mann-Whitney U-tests were performed to compare surgery duration between the two surgeons. Recovery quality scores between groups were compared using χ2 test of homogeneity. Recovery quality scores were adjusted into binary categories where scores of 1 and 2 were categorised as 'unacceptable' and scores 3-5 were categorised as 'acceptable' recoveries to facilitate statistical analysis using χ2 tests. Statistical significance was set at *P*≤0.05. A power calculation (G\*Power version 3.0.10) was performed based on data from a previous study using the 'quad' protocol with atipamezole in male cats at the same hospital.4 This indicated that 32 cats per group would give 80% power to detect a difference of 20 mins in recovery time (f = 0.3).

**Results**

The majority (n = 126) of the cats presented for castration were domestic shorthaired or longhaired and only two cats were pedigree breeds (one Ragdoll and one Persian). Of all the cats enrolled in the study, 85 were public owned and 43 were strays for re-homing. Of the public owned cats, 66% were from multi-cat households. Overall median (IQR) age and body weight of cats included in the study was 8 (3-24) months and 2.87 (1.23-3.5) kg respectively. Details of abnormalities detected in ASA 2 cats during history taking and pre-anaesthetic examination are displayed in Table 1. Demographic data including median (IQR) age and body weight of the study cats in each of the atipamezole treatment groups are displayed in Table 2. Despite attempts to randomise allocation of study cats to atipamezole treatment groups, median age and body weight were significantly lower in group 1ATI40 compared to group 2.5ATI20 (*P* = 0.015 and 0.019 respectively). Mean ± SD temperature data at each of the four time points in the four atipamezole treatment groups are displayed in Table 3. There were no significant differences in auricular temperature between atipamezole treatment groups at any of the four time points. However, significant differences in temperature at different time points within treatment groups were observed. T4 was significantly lower than T1 (*P*<0.001), T2 (*P*<0.001) and T3 (*P*<0.001) within all four atipamezole treatment groups. For atipamezole treatment groups 1ATI20 and 2.5ATI20, T3 was significantly lower than T2 (*P* = 0.001 and 0.007 respectively). Additionally for group 1ATI20, T3 was significantly lower than T1 (*P* = 0.003) but no significant differences between T2 and T1 were identified within any treatment group.

Mean ± SD preparation time, surgery time, injection to sternal recumbency, injection to first standing and recovery quality scores are displayed in Table 4. There was no significant difference in preparation time or surgery time between the atipamezole treatment groups. Cats in group 2.5ATI20 achieved sternal recumbency significantly faster than cats in group 1ATI20 (*P* = 0.033) but there were no significant differences in time to sternal recumbency between any other treatment groups. There were no significant differences in time from injection to first standing or recovery quality score between atipamezole treatment groups.

One surgeon (KH) performed the majority of the castrations (n = 118) and the other surgeon (AE) performed 10 of the castrations, with mean ± SD surgery times of 2.8 ± 0.8 mins and 3.1 ± 0.9 mins respectively. There was no significant difference in surgery time between the surgeons. Peri-operative adverse events or complications detected in study cats are displayed in Table 5. No major adverse events were observed and all public owned cats were discharged from the hospital on the same day.

**Discussion**

The purpose of this study was to attempt to establish the optimum dosage and timing of administration of atipamezole in cats undergoing a short general anaesthetic incorporating ketamine in order to provide the shortest recovery possible without unacceptably compromising recovery quality.

The results from this study demonstrated that cats receiving an atipamezole: medetomidine dose ratio of 2.5:1 achieved sternal recumbency significantly faster than cats receiving an atipamezole:medetomidine dose ratio of 1:1 after 20 mins. However, there were no significant differences in time to sternal recumbency between any other treatment groups and no significant differences in time from injection to first standing or recovery quality score between treatment groups. Therefore, these results would suggest that atipamezole administration after 20 mins does not confer any benefit in terms of reducing recovery time but neither was recovery quality adversely affected compared to when administered after 40 mins following datasheet recommendations with concurrent ketamine administration. In addition, the results of this study would suggest that an atipamezole:medetomidine dose ratio of 2.5:1 is more effective than 1:1 in reducing recovery time regardless of the timing of atipamezole administration (although only reaching statistical significance for time to sternal recumbency when atipamezole was administered after 20 mins).

This study also demonstrated a significant reduction in auricular temperature from immediately prior to surgery up to 40 mins post general anaesthetic induction, regardless of atipamezole treatment group. These results concur with previous feline studies in which body temperature was measured after medetomidine administration.22,23 However, neither dosage nor timing of administration of atipamezole appeared to affect temperature as no significant differences in auricular temperature were identified between treatment groups at any of the four time points. We chose to measure auricular temperature in this study as we anticipated that this was likely to be better tolerated in the recovery period than rectal thermometry and therefore less likely to influence recovery time and quality. A previous study comparing both methods of temperature measurement concluded that auricular thermometry was a reliable alternative to rectal thermometry in healthy cats and was well tolerated in a greater proportion of cats than rectal thermometry (93.1% versus 72.4% respectively).24 Another study reported a rectal-auricular temperature difference range of -1.6°C to 3°C in cats and concluded that these two temperature measurement methods should not be used interchangeably.25 The same study also reported that axillary temperature measurement was better tolerated than both rectal and auricular methods and agreed more closely with rectal temperature measurements compared to the auricular method.25 In the present study, one person (NB) performed all auricular temperature measurements and the same method of temperature measurement was implemented consistently throughout the duration of the study. Therefore, analysis of temperature trends over time and between cats in different treatment groups should be valid. Subjectively, auricular temperature measurement was not deemed to affect recovery time or quality and appeared to be well tolerated in our population of healthy cats undergoing and recovering from general anaesthesia. However, axillary temperature measurement could have perhaps been considered as an alternative.

Buprenorphine was incorporated into the 'quad' protocol in this study as has been described previously.1,4,20 However, a recent study comparing buprenorphine to methadone in the 'quad' for cats undergoing ovariohysterectomy demonstrated more efficacious analgesia with methadone than buprenorphine.26 Therefore, although the provision of multimodal analgesia with medetomidine, ketamine, buprenorphine and meloxicam in this study was deemed likely to be sufficient for castration, methadone could have been considered as an alternative to buprenorphine.

Adverse effects observed in this study were limited and none were life threatening. Dysphoria in recovery, characterised by the presence of disorientation, abnormal movements including pacing, mydriasis, vocalisation or oversensitivity to stimuli, was the most frequent adverse event observed with an incidence of 6.25%. This could not be attributed to a particular atipamezole treatment group but the fact that all cases occurred in cats receiving an atipamezole:medetomidine dose ratio of 2.5:1 regardless of timing of administration is perhaps noteworthy. Several drugs included in the 'quad' protocol may have been responsible for affecting the cats' behaviour in recovery. Ketamine has previously been reported to result in ataxia, reduced ability to walk, pacing, sudden jerky movements and increased sensitivity to touch in cats recovering from general anaesthesia.12,17,18 Midazolam has also been reported to cause ataxia and an abnormal arousal state in cats.27 However, midazolam was administered to awake cats and in higher doses than used in the current study. Overall, there was no significant difference in recovery quality scores between the atipamezole treatment groups.

Four cats required administration of 0.5-1.5% isoflurane via mask to maintain an adequate depth of anaesthesia. The most likely explanation for this is that these cats did not receive the full 'quad' dose IM. It was considered unlikely that administration of up to 1.5% isoflurane for up to 3 mins would have a significant effect on recovery time or quality. Recovery times to sternal recumbency and standing in these cats fell within 2 SD of the mean for their atipamezole treatment group. One of the cats that received isoflurane was assigned a recovery quality score of 1 (poor) but the other three cats were deemed to have good or very good recovery quality. The number of cats receiving isoflurane was too low to determine whether isoflurane negatively impacted recovery quality in this study. One cat had abnormal, atrophied testes which made surgery more technically challenging. However, although surgical time for this cat fell outside 2 SD of the group mean, time to sternal recumbency, time to first standing and recovery quality fell within 2 SD of the group means, so data from this animal were still included in statistical analysis. One cat was observed to pass a small amount of diarrhoea following induction of general anaesthesia. However, this cat was from a multi-cat household where other cats had been reported to have mild diarrhoea. Therefore, this was considered most likely to be caused by an underlying health problem rather than an adverse reaction to general anaesthesia.

Two cats in the study had osseous fractures: a chronic distal radius fracture (weight bearing) and a proximal tail fracture. These cats were randomly allocated to groups 2.5ATI40 and 2.5ATI20 respectively. Times to sternal recumbency and standing for both cats fell within 2 SD of the group means so their data were included in statistical analyses.

One experienced nurse monitored and scored all of the recoveries in this study and was blinded to the atipamezole treatment group. It was not possible to completely disguise administration of atipamezole by IM injection without use of placebo injections at the other time points. However, the fact that kennels were opened to allow auricular temperature measurements by the anaesthetist at these time points was thought to help to disguise the timing of atipamezole injection from the nurse monitoring recoveries. This was considered preferable to administering an additional and potentially painful IM injection of saline to each cat without any clinical benefit.

There are several limitations to this study. Despite attempts to randomise allocation of cats to each treatment group, there was an uneven age and body weight distribution between groups with lower median age and body weights in both groups receiving a 1:1 dose ratio of atipamezole:medetomidine. It is possible that this could have affected our results as it has previously been demonstrated that cats ≤ 6 months old recovered more quickly than cats > 6 months old using the 'quad' anaesthetic protocol.4 However, although median age of cats was lower in the 1:1 atipamezole:medetomidine dose ratio groups, mean recovery times were shorter in both of the groups that received a dose ratio of 2.5:1. Perhaps a greater difference in recovery times would have been observed if there had been a more even age distribution between treatment groups.

Another potential limitation was the fact that 66% of cats participating in the study were from multi-cat households and some were poorly socialised. It is possible that this may have affected their behaviour in the hospital during recovery, potentially affecting recovery time and quality. As cats were allocated to treatment groups based on order of admission, it is possible that admission of several cats from the same litter or similar age cohorts may have affected the randomisation process.

The recovery quality scoring system used in this study was subjective and no validated scoring systems exist for cats. The recovery quality scoring scale was chosen because we wanted a simple, user friendly scoring system that could be implemented quickly and easily in a clinical setting. However, the scoring system was adapted from a feline study using propofol which did not form part of the anaesthetic protocol used in this study.21 Another recovery quality scoring system for cats comparing alfaxalone to ketamine and diazepam has been reported.17 However, this system requires assessment of sensitivity to touch, sound and light which may have influenced time to sternal recumbency and first standing so we opted for a scoring system that required observation only.

Although it would have been preferable to have only one surgeon for the entire duration of the study, two surgeons performed the castrations due to constraints of the clinic rota that could not be avoided. However, both were experienced surgeons and no significant differences in surgery duration between the two were observed. Therefore, this was not considered to be an important cofounding factor in our study.

We did not include a control group in which cats received no atipamezole. It has previously been demonstrated that spontaneous recovery time after general anaesthesia for cat castration with the 'quad' was significantly longer compared to when atipamezole was administered.4 As it has also been shown that the majority of peri-anaesthetic deaths in cats occur during the recovery period,10 it was considered unethical to knowingly prolong the recovery period by withholding atipamezole from cats in one of the treatment groups in this study.

Differences in mean time to sternal recumbency and standing between treatment groups were 13 and 11 mins respectively which was not considered clinically relevant. This study had 80% power to detect mean difference in time to sternal recumbency of 20 mins and therefore was underpowered to establish whether there were any real differences between atipamezole treatment groups. A greater sample size may have answered the question of whether time to sternal recumbency was truly different with different atipamezole treatment regimes.

**Conclusions**

Atipamezole administration after 20 mins did not reduce recovery time but neither was recovery quality adversely affected compared to when administered at the current datasheet recommendation of 40 mins with concurrent ketamine usage. The results of this study also suggest that an atipamezole:medetomidine dose ratio of 2.5:1 is more effective than 1:1 in reducing recovery time regardless of timing of administration, although this only reached statistical significance for time to sternal recumbency when atipamezole was administered after 20 mins.

**Acknowledgements**

The authors would like to kindly thank Kayleigh Hill, Jodie Hartley, Albert Holgate and Amy Edwards for their invaluable assistance with data collection at the RSPCA GMAH.

**Conflicts of interest**

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The authors received no financial support for the research, authorship and/or publication of this article.

**Ethical Approval**

This work involved the use of client-owned animals outside of established internationally recognised high standards (‘best practice’) of individual veterinary clinical patient care. The study therefore had Ethics Approval from an established committee as stated in the manuscript.

**Informed Consent**

Informed Consent (either verbal or written) was obtained from the owner or legal guardian of all animals described in this work for the procedure undertaken. No animals or humans are identifiable within this publication, and therefore additional Informed Consent for publication was not required.

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**Table 1** Abnormalities detected in American Society of Anesthesiologists' (ASA) classification 2 study cats from history and pre-anaesthetic examination.

|  |  |
| --- | --- |
| **Abnormality** | **Cats affected (n)** |
| Fleas/flea dirt (*Ctenocephalides felis*) | 46 |
| Tapeworm (*Dipylidium caninum*) | 9 |
| Ear mites (*Otodectes cynotis*) | 8 |
| Mild diarrhoea | 7 |
| Ocular disease (mucoid conjunctivitis, corneal scarring or symblepharon) | 5 |
| Serous nasal discharge +/- sneezing | 3 |
| Systolic heart murmur | 3 |
| Cat bite abscess/wound | 3 |
| Osseous fracture | 2 |
| FIV positive on FASTest\* | 2 |
| Alopecia | 1 |
| Pododermatitis | 1 |
| Gingivitis/dental disease | 1 |
| Ticks (*Ixodes* spp.) | 1 |

\*FASTest (Megacor)

FIV = feline immunodeficiency virus

**Table 2** Age and body weight data for study cats in each of the four treatment groups.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Atipamezole treatment group (n=32)** | | | |
| **Patient variable** | **1ATI20** | **2.5ATI20** | **1ATI40** | **2.5ATI40** |
| Age (months) | 6 (3-15) | 16 (6-27) \* | 4 (2-12) \* | 12 (3-36) |
| Body weight (kg) | 2.33 (1-3.49) | 3.29 (2.46-3.86) † | 1.63 (1.1-3.22) † | 3.19 (1.38-3.6) |

Data are presented as median (IQR).

Group 1ATI20 = 600µg/m2 atipamezole after 20 mins; group 2.5ATI20 = 1.5mg/m2 atipamezole after 20 mins; group 1ATI40 = 600µg/m2 atipamezole after 40 mins; group 2.5ATI40 = 1.5mg/m2 atipamezole after 40 mins.

\* denotes significant difference between treatment groups for age (P≤0.05).

† denotes significant difference between treatment groups for body weight (P≤0.05).

**Table 3** Auricular temperature data for study cats in each of the four treatment groups at four different time points.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Atipamezole treatment group (n=32)** | | | |
| **Auricular temperature (°C)** | **1ATI20** | **2.5ATI20** | **1ATI40** | **2.5ATI40** |
| Before surgery (T1) | 37.4 ± 0.7 | 37.6 ± 0.7 | 37.4 ± 0.8 | 37.4 ± 0.8 |
| End of surgery (T2) | 37.4 ± 0.6 ‡ | 37.6 ± 0.7 ‡ | 37.4 ± 0.8 | 37.4 ± 0.8 |
| 20 mins after 'quad' (T3) | 37.1 ± 0.7 \*† | 37.4 ± 0.7 † | 37.3 ± 0.7 | 37.2 ± 0.9 |
| 40 mins after 'quad' (T4) | 36.6 ± 0.6 \*†‡ | 37.0 ± 0.7 \*†‡ | 36.8 ± 0.9 \*†‡ | 36.8 ± 0.9 \*†‡ |

Data are presented as mean ± SD.

Group 1ATI20 = 600µg/m2 atipamezole after 20 mins; group 2.5ATI20 = 1.5mg/m2 atipamezole after 20 mins; group 1ATI40 = 600µg/m2 atipamezole after 40 mins; group 2.5ATI40 = 1.5mg/m2 atipamezole after 40 mins.

\* denotes significant difference in auricular temperature from pre-surgery auricular temperature (T1) within the same atipamezole treatment group (P≤0.008 with Bonferroni adjustment).

† denotes significant difference in auricular temperature from auricular temperature at end of surgery (T2) within the same atipamezole treatment group (P≤0.008 with Bonferroni adjustment).

‡ denotes significant difference in auricular temperature from auricular temperature 20 mins after 'quad' injection (T3) within the same atipamezole treatment group (P≤0.008 with Bonferroni adjustment).

**Table 4** Study variables measured in each of the four atipamezole treatment groups.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Atipamezole treatment group (n=32)** | | | |
| **Study variable** | **1ATI20** | **2.5ATI20** | **1ATI40** | **2.5ATI40** |
| Preparation time (mins) | 9.7 ± 1.9 | 10.9 ± 2.5 | 10.1 ± 2 | 10.2 ± 2.1 |
| Surgery time (mins) | 2.9 ± 0.6 | 2.7 ± 0.6 | 2.8 ± 1 | 2.7 ± 0.9 |
| Injection to sternal recumbency (mins) | 65.7 ± 24.7 \* | 52.9 ± 22.3 \* | 60.4 ± 22 | 52.9 ± 10 |
| Injection to first standing (mins) | 85.2 ± 34.7 | 77.9 ± 43.2 | 81.5 ± 40.3 | 74.5 ± 33.4 |
| Recovery quality score | 3.7 ± 1.2 | 3.5 ± 1.3 | 3.7 ± 1.2 | 3.5 ± 1.2 |

Data are presented as mean ± SD.

Group 1ATI20 = 600µg/m2 atipamezole after 20 mins; group 2.5ATI20 = 1.5mg/m2 atipamezole after 20 mins; group 1ATI40 = 600µg/m2 atipamezole after 40 mins; group 2.5ATI40 = 1.5mg/m2 atipamezole after 40 mins.

\* denotes significant difference in time from injection to sternal recumbency between atipamezole treatment groups (P≤0.05).

**Table 5** Peri-operative adverse events/complications detected in study cats.

|  |  |  |
| --- | --- | --- |
| **Adverse event/complication** | **Cats affected (n)** | **Treatment group of affected cats** |
| Dysphoria in recovery | 8 | 2.5ATI20 (5), 2.5ATI40 (3) |
| Requirement for isoflurane | 4 | 1ATI20 (3), 2.5ATI40 (1) |
| Abnormal/atrophied testes | 1 | 2.5ATI40 |
| Diarrhoea | 1 | 1ATI20 |

Group 1ATI20 = 600µg/m2 atipamezole after 20 mins; group 2.5ATI20 = 1.5mg/m2 atipamezole after 20 mins; group 1ATI40 = 600µg/m2 atipamezole after 40 mins; group 2.5ATI40 = 1.5mg/m2 atipamezole after 40 mins.