Combinations of dexmedetomidine and alfaxalone with butorphanol in cats: application of an innovative stepwise optimization method to identify optimal clinical doses for intramuscular anaesthesia.

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Abstract

Objectives The aim of this study was to optimize dexmedetomidine and alfaxalone dosing, for intramuscular administration with butorphanol, to perform minor surgeries in cats.

Methods Initially, cats were assigned to one of 5 groups, each composed of 6 animals and receiving, in addition to 0.3 mg/kg butorphanol IM, one of the following: A: 0.005 mg/kg dexmedetomidine, 2 mg/kg alfaxalone; B: 0.008 mg/kg dexmedetomidine, 1.5 mg/kg alfaxalone; C: 0.012 mg/kg dexmedetomidine, 1 mg/kg alfaxalone; D: 0.005 mg/kg dexmedetomidine, 1 mg/kg alfaxalone; and E: 0.012 mg/kg dexmedetomidine, 2 mg/kg alfaxalone. Thereafter, a modified "direct search" method, conducted in a stepwise manner, was used to optimize drugs dosing. The quality of anaesthesia was evaluated on the basis of composite scores (one for anaesthesia and one for recovery), of Visual Analogue Scales, and of propofol requirement to suppress spontaneous movements. The medians or means of these variables were used to rank the treatments: "unsatisfactory" and "promising" combinations were identified to calculate, through the equation first described by Berenbaum in 1990, new dexmedetomidine and alfaxalone doses to be tested in the next step. At each step, 5 combinations (one new plus the best previous four) were tested.

Results None of the tested combinations resulted in adverse effects. Four steps and 120 animals were necessary to identify the optimal drug combination (0.014 mg/kg dexmedetomidine, 2.5 mg/kg alfaxalone and 0.3 mg/kg butorphanol).

Conclusions and relevance The investigated drug mixture, at the doses found with the optimization method, is suitable for cats undergoing minor clinical procedures.

Keywords: alfaxalone, butorphanol, cats, dexmedetomidine, injectable anaesthesia, optimization method

Introduction

In several Swiss veterinary practices, intramuscular injectable anaesthesia is preferred over intravenous and inhalational techniques for feline patients undergoing minor clinical procedures. The rationale for this tendency may be the common belief, among general practitioners, that deep sedation is safer than inhalational anaesthesia. As an alternative explanation, owing to the uncooperative nature of feline patients, intravenous catheterization can be challenging in non-sedated cats and this may prevent veterinarians from attempting physical restraint.

To date, several drug combinations have been investigated for feline intramuscular anaesthesia. Commonly used protocols often include an alpha$_2$-adrenoreceptor agonist to produce reliable sedation, an opioid derivative to provide some analgesia, and ketamine owing to its anaesthetic and analgesic effects.

Among alpha$_2$-adrenoreceptor agonists, dexmedetomidine - the active enantiomer of racemic medetomidine - has recently been licensed for administration to cats in some countries and has gained wide popularity in general practice owing to its convenience, ease of administration and possibility to antagonize its effects. Several investigators found that dexmedetomidine is a reliable sedative in feline patients and produces dose-dependent analgesia and muscle relaxation with acceptable side effects.[1,2] These features make this compound suitable as sole agent for minor clinical procedures associated with mild nociceptive stimulation.

Butorphanol is a synthetic opioid with agonistic activity at κ-opioid receptors and antagonistic effects at μ receptors.[3] Because in most countries is not listed among controlled substances, it is very often preferred over more potent opioid derivatives by many practitioners in Europe. After intramuscular administration, butorphanol decreased the thermal nociceptive threshold and produced short lasting and variable analgesia in cats.[4,5] Its combination with dexmedetomidine resulted in greater sedation and more profound muscle relaxation, but not faster onset of recumbency, than dexmedetomidine alone in experimental cats.[6]

Ketamine is a dissociative anaesthetic with high bioavailability and short onset of action after intramuscular administration.[7] Its use has been widely investigated in feline patients.[8-12] However, its addition to dexmedetomidine and butorphanol was found to prolong the time to recovery.[6]

As an alternative to ketamine, the inclusion of alfaxalone in alpha$_2$-adrenoreceptor agonists-opioids combinations may offer some advantages for cats undergoing minor procedures, namely short duration of the anaesthetic effect, high therapeutic index, and excellent muscle relaxation.[13] Additionally, clinical studies investigating the effects of subcutaneous alfaxalone prepared in 2-hydroxypropyl-beta cyclodextrin solution seem to indicate a rapid systemic absorption when routes of administration other than intravenous injection are used.[14,15]

On the basis of the current literature, dexmedetomidine-butorphanol-alfaxalone intramuscular combination can be considered a promising anaesthetic technique for cats undergoing minor clinical procedures. The optimal dose combination of these three drugs is unknown and unlikely to be identified by randomized controlled study, due to the numbers of animals required for all possible combinations to be investigated. For this reason, we applied a modified "direct search" model,[16] an innovative optimization method based on a mathematical algorithm, whose main advantage is that a limited number of dose combinations - and therefore a limited number of patients – require investigation.

The aim of the current study was to optimize the doses of intramuscular dexmedetomidine, butorphanol and alfaxalone, in terms of reliability and rapid onset of anaesthesia and absence of peri-anaesthetic complications, in domestic cats undergoing minor surgical procedures.

Materials and methods

Study design and ethical approval

This study was designed as an investigator-blind, randomized, prospective clinical trial, and performed with permission of the local Ethics Committee for Animal Experimentation (Canton of Berne, Switzerland, license number: 22197) and written informed owner consent.

Animals

One hundred and twenty client-owned adult cats admitted to the Veterinary Teaching Hospital of the University of Berne from January 2013 to January 2015 for minor surgical procedures (wound curettage followed by bandage/wound dressing change, or control radiographic exam followed by external pin removal) were enrolled in the study. Food, but not water was withheld for 12 hours prior to anaesthesia. Cats underwent a routine pre-anaesthetic physical examination in order to assess the health status. In cooperative animals, in which venipuncture and blood sampling could be performed without sedation, basic blood parameters (hematocrit, total proteins and electrolytes and serum creatinine levels) were also assessed. Exclusion criteria were pregnancy, systemic diseases, impaired cardiovascular function, elderly (more than 8 years) and ASA risk classification grade greater than II.

The animals were randomly assigned to one of five treatment groups. A manual randomization technique was used (drawing group assignment from an opaque envelope).

Treatment groups

Cats were injected intramuscularly (IM) with a mixture of dexmedetomidine (Dexdomitor; Pfizer), alfaxalone (Alfaxan; Vétoquinol) and butorphanol (Morphasol; Graeub), mixed in one syringe, at one of the following dose-combinations:

- GROUP A: 0.005 mg/kg dexmedetomidine, 2 mg/kg alfaxalone and 0.3 mg/kg butorphanol.
- GROUP B: 0.008 mg/kg dexmedetomidine, 1.5 mg/kg alfaxalone and 0.3 mg/kg butorphanol.
- GROUP C: 0.012 mg/kg dexmedetomidine, 1 mg/kg alfaxalone and 0.3 mg/kg butorphanol.
- GROUP D: 0.005 mg/kg dexmedetomidine, 1 mg/kg alfaxalone and 0.3 mg/kg butorphanol.
- GROUP E: 0.012 mg/kg dexmedetomidine, 2 mg/kg alfaxalone and 0.3 mg/kg butorphanol.

Each treatment group was composed of 6 cats. The rationale for choosing this number is explained in the Appendix (Supplementary file). The drugs doses for groups A-E were selected on the basis of the following criteria: clinical experience of the study's designer, existing literature and manufacturers' recommendations for the species. In order to avoid iatrogenic muscular lesions, the volume of injectate exceeding 1 ml was equally divided into two injection sites.

Anaesthetic Procedure

Prior to anaesthesia, baseline values for heart rate (HR), respiratory rate (RR) and rectal body temperature were recorded. To evaluate the baseline temperament and behavior,

each cat was assigned to one of three categories: tranquil and quiet, stressed or scared, and aggressive.

The time to anaesthesia, defined as the minutes elapsing from injection to lateral recumbency, was recorded.

The occurrence of undesired effects after IM injection, namely vomitus, hypersalivation, respiratory depression and/or increased muscular tone, was noted. A score ranging from 0 to 4 (Undesired Effects Score) was assigned to each cat, with 0 being “none of the listed side effects was observed” and 4 being “all the listed side effects were observed”.

Ten minutes after IM injection, a catheter was placed into the right or left cephalic vein, or in a peripheral vein of one hind limb if judged more appropriate with respect to the clinical procedure.

The observer evaluated the degree of reaction to IV catheter placement by assigning a score, ranging from 0 to 4, with 0 being “no reaction”, 1 “mild reaction” (attempts to withdraw the limb), 2 “moderate reaction” (vocalization and and/or hissing, movements, one person needed for physical restraint) and 3 “aggressive reaction” (vocalization and/or hissing, attempts to bite, two people required for adequate physical restraint).

A score ranging from 0 to 5 (Composite Anaesthesia Score), as described by Biermann and colleagues,[11] was assigned every 5 minutes until completion of the clinical procedures. The latter were started as soon as the cats became laterally recumbent.

During anaesthesia, the cats were instrumented with a pulse-oximeter (Microcap plus; Oridion), an electrocardiograph (Schiller AT-4; Medical Device Depot) and a Doppler (Model 811B; Parks Medical Electronics) for non-invasive arterial blood pressure measurement. The respiratory rate was determined by visual examination of the thorax. Arterial oxygen saturation, HR, RR and systolic arterial blood pressure (SAP) were manually recorded every 5 minutes.

The depth of anaesthesia was assessed on the basis of commonly used clinical descriptors (presence or absence of corneal and palpebral reflexes and degree of muscular relaxation).

If major movements, defined as flexion/extension of the limbs and/or of the neck, and/or lifting of the head, were observed during the surgical procedure, propofol (Propofol 1%; Fresenius Kabi) was administered IV in steps of 1.5 mg/kg. The number of propofol boli given to each cat, as well as the time of administration, was recorded. All cats received oxygen supplementation by mask with the flow rate set to deliver 2 L/min, and a balanced crystalloids' solution (Ringer-Lactat; Baxter) was administered intravenously (IV) at the rate of 5 ml/kg/h.

In the event of bradycardia (HR < 100 bpm) with normo- or hypotension (SAP < 100 mmHg) and with or without ventricular escape rhythm, glycopyrrolate (Robinul; Sintetica SA), 0.01 mg/kg, was given IV. In the event of moderate sinus bradycardia (HR 99-70 bpm) accompanied by hypertension (SAP > 150 mmHg), no anticholinergic

was given and the rhythm was watched closely to detect any change from the baseline. Finally, if severe bradycardia (HR < 70 bpm), or moderate bradycardia accompanied by hypertension and ventricular escape rhythm, were observed, atipamezole (Antisedan; Provet) was administered IM at five times the dexmedetomidine dose. The duration of the clinical procedure was recorded. At the end of the procedure, a 10 cm Visual Analogue Scale (VAS), with 0 being labeled as worst possible and 10 as best possible, was used for an overall, subjective evaluation of the quality of anaesthesia. Thereafter, unless it had been necessary to antagonize the dexmedetomidine before the completion of the procedure, the cats were injected with IM atipamezole. The time to recovery, defined as the minutes elapsed from atipamezole injection to active interaction, was recorded. The rectal body temperature was measured at the end of anaesthesia.

The quality of recovery was assessed by using a Composite Recovery Score, ranging from 0 to 14 and based on the following descriptors: comfort, coordination, vocalization, movement during sternal recumbency, locomotor activity and scratching and grooming, as described by Biermann and others.[11] Additionally, a 10 cm VAS, with 0 labeled as worst possible recovery and 10 labeled as best possible recovery, was used. All the assessments were performed by the same anaesthetist (C.A.), who also injected the cats and was blind to the treatment.

Optimization Procedure

The optimization procedure used in this study is a modification of the "direct search" method as described by Berenbaum and colleagues[17] and applied by Sveticic in a clinical trial involving human patients.[16] A detailed description of the methods and of the equations used is provided in the Appendix (Supplementary file).

The optimization of the drug combination was conducted in a stepwise manner, and the treatment groups tested at each step were defined as a *complex*. The initial 5 drugs combinations tested composed the complex number 1. Within each complex, the best treatment groups in terms of quality of anaesthesia (greatest median Composite Anaesthesia Scores, mean VAS Anaesthesia scores and VAS Recovery scores, and lowest medians of number of propofol boli and Composite Recovery Scores) and minimal side effects (lowest median Undesired Effects Scores) were identified. These groups were defined "promising groups", whereas the remaining ones were classified as "unsatisfactory groups". The new complex, to be tested in other 30 cats (6 per each group), was composed of four of the previously tested treatments (all but the worst one) plus a fifth one, generated by applying a mathematical model on the basis of the results of the previous step (Appendix). Data obtained from complex 2 were analyzed as previously described and used to generate a new complex until an optimal drug doses combination was found. For alfaxalone, the maximal dose to be used was fixed at 2.5 mg/kg.

The optimization procedure was considered completed when the scores obtained from the new drug combination were not better of those of the previously tested treatments, and when these results were consistent for three consecutive steps. The dose searching method was to conclude also in case the mathematical model generated a drug combination which had already been tested in at least one of the previous steps.

Statistics

Commercially available software (NCSS-2007; NCSS and SigmaStat and SigmaPlot 12; Systat Software Inc.) were used. Normality of data was tested with the Shapiro-Wilk tests. Descriptive statistics was used for comparison of treatment groups with respect to the following variables: Composite Anaesthesia Score, VAS Anaesthesia and Recovery scores, Composite Recovery Scores, medians of number of propofol boli, and Undesired Effects Scores. The cardiorespiratory variables (HR, RR and SAP) were analyzed with repeated measures ANOVA, followed by either the Bonferroni or the Tukey-Kramer multiple comparison test. The duration of the clinical procedure, the time to anaesthesia and the time to recovery were analyzed with the Kruskal-Wallis one way ANOVA on ranks, followed by the Dunn's test. One way ANOVA on ranks was used to compare the baseline rectal body temperatures of each group with the values measured at recovery. The Chi-Square test was used to compare the distribution of the two clinical procedures between treatment groups.

P values < 0.05 and Z values > 1.96 were considered statistically significant.

Results

Data for body weight, age and rectal body temperature were normally distributed.

Four complexes, 120 cats and 8 groups, 5 of which included in complex 1 and three new ones (N1, N2 and N3; Table 1), were necessary to establish the optimal drug combination, which was 0.014 mg/kg of dexmedetomidine, 2.5 mg/kg of alfaxalone and 0.3 mg/kg of butorphanol.

The optimization procedure concluded after completion of data collection for complex 4, as the fourth new treatment group obtained through the mathematical model was the same as N2, which had been previously tested.

The cats had a body weight of 4.2 (± 0.8) kg, were aged 4.4 (± 1.6) years and were 61 males (55 of which castrated) and 59 females (all of which spayed). The 8 treatment groups did not differ with respect to type of clinical procedure (P = 0.66; Table 2), duration of the latter (P = 0.17; Figure 1), time to anaesthesia (P = 0.79; Table 3) and time to recovery (P = 0.29; Table 3). Hypertension and bradycardia were observed in the 11% and 25% of the cats, respectively. However, any statistically significant difference in HR (P = 0.76), RR (P = 0.32), SAP (P = 0.35) and rectal body temperature (P = 1.2) was detected, neither between treatments nor between time points (Figure 2, 3 and 4).

All 8 drug combinations resulted in a degree of unresponsiveness sufficient to allow for intravenous catheterization ten minutes after injection, so that in all cats physical restraint was unnecessary. None of the cats required administration of glycopyrrolate or atipamezole before the end of the clinical procedure. None of the tested treatments resulted in clinically relevant side effects and anaesthesia and recovery were uneventful for all the cats enrolled in the study. The medians or means of VAS Anaesthesia, Composite Anaesthesia Score, number of propofol boli, Undesired Effects Score, VAS Recovery, and Composite Recovery Score, are summarized in Table 4.

Table 1 Doses for intramuscular alfaxalone (A), dexmedetomidine (D) and butorphanol (B), expressed in mg/kg, for 8 treatment groups

GROUP	A	D	B
A	2	0.005	0.3
B	1.5	0.008	0.3
C	1	0.012	0.3
D	1	0.005	0.3
E	2	0.012	0.3
N1	2.5	0.009	0.3
N2	2.5	0.014	0.3
N3	2.5	0.010	0.3

Table 2 Number of cats per group with one of three types of baseline temperament, undergoing one of two types of minor surgical procedures

	PROCEDURE		TEMPERAMENT		
GROUP	**WC (n)**	**RX (n)**	**TQ (n)**	**SS (n)**	**A(n)**
A (n = 18)	8	10	5	8	5
B (n = 6)	2	4	2	3	1
C (n = 24)	12	12	5	13	6
D (n = 12)	8	4	1	8	3
E (n = 24)	13	11	8	10	6
N1 (n = 18)	10	8	8	5	5
N2 (n = 12)	8	4	3	8	1
N3 (n = 6)	4	2	2	3	1
TOTAL (120)	65	55	34	58	28

285

286 WC = wound curettage followed by bandage/dressing change; RX = control RX followed by
287 external pins removal; TC = tranquil and quiet; SS = stressed or scared; A = aggressive.

288

289 **Table 3** Medians and ranges [max-min] of time to anaesthesia, defined as the minutes
290 elapsed from IM injection to lateral recumbency, and time to recovery, defined as the
291 minutes elapsed from atipamezole IM injection to active interaction

GROUP	Time to anaesthesia	Time to recovery
A	6.5 [2-20]	12 [5-35]
B	5 [5-13]	11.5 [2-16]
C	5 [1-20]	7 [1-47]
D	7.5 [2-12]	15 [5-30]
E	5 [1-20]	7 [2-75]
N1	5 [2-20]	18.5 [5-40]
N2	5 [1-11]	9.5 [2-35]

N3	4 [2-8]	15.5 [2-32]

292

293 **Table 4** Variables for complex 1, 2, 3 and 4, presented as either means‡ or medians*.

294 The worst treatment group (to be excluded from the optimization process) is colored in

295 red, while the best final treatments are in bold characters.

Complex	Group	VAS A‡	CAS*	PropB *	UES‡	VAS R*	CRS*	Final score
1	A	8.78	5	0.5	0	7.80	2.5	P
1	B	4.28	3.50	3	0	6.50	3	U
1	C	7.75	4.5	1.5	0	6.10	3	U
1	D	6.15	4	1	0	7.50	2	U
1	E	9.57	5	0	0	8.53	1	P
2	A	9.00	4.5	1	0	7.90	2	U
2	C	7.80	4.5	1	0	8.00	2	U
2	D	7.55	4.5	2	0	7.10	2	U
2	E	9.25	4.5	0	0	9.15	0.5	P
2	N_1	9.50	5	0	0	9.20	0	P
3	A	8.30	4.5	1	0	7.15	2.5	U
3	C	8.35	4.75	1	0	8.60	2	U
3	E	9.45	5	0.5	0	8.3	2	U
3	N_1	9.40	5	0.5	0	9.7	1	P
3	N_2	9.75	5	0	0	9.65	1.5	P
4	C	7.33	4.5	1	0	8.12	2.5	U
4	**E**	**8.97**	**5**	**0.5**	0	**9.12**	**2**	**P**
4	**N_1**	**9.32**	**5**	**0**	0	**9.37**	**1.5**	**P**
4	**N_2**	**9.52**	**5**	**0**	0	**9.12**	**1**	**P**
4	N3	9.18	5	0	0	7.56	3	U

296 VAS A = VAS Anaesthesia; CAS = Composite Anaesthesia Score; PropB = number of
297 propofol boli; UES = Undesired Effects Score; VAS R: VAS Recovery; CRS =
298 Composite Recovery Score; P = promising complex; U = unpromising complex.
299
300
301 **Discussion**
302 The main finding of this study is that the optimal alfaxalone–dexmedetomidine–
303 butorphanol combination established by applying the optimization method resulted in
304 reliable, rapid onset, and uneventful anaesthesia in cats undergoing minor surgical
305 procedures.
306 The modified version of the optimization method as used in this study was feasible,
307 applicable to the clinical setting and compatible with the routine of a busy veterinary
308 hospital.
309 The rational for using a relatively high number of cats was the premise that, for an
310 objective and unbiased data collection, the investigator needed to be blind to the
311 treatments at each step of the search process. This implied the repetition of the good
312 treatments, so that each complex could be composed of 5 groups. A different study
313 design, with the investigator responsible for data collection completely unaware of the
314 study phases, would have allowed the avoidance of such repetition, making the all
315 process easier and less time consuming.

316 None of the cats had complications. However, mild hypertension and bradycardia were
317 observed in some animals, a finding which limits the use of the anaesthetic protocol to
318 healthy cats.
319 Providing a definition of bradycardia and hypertension in anaesthetized cats is
320 challenging owing to the conflicting results of the currently published work. It was
321 reported that feline patients have considerably lower heart rates when the measurements
322 are taken in home environment compared to the hospital, and that normal values for HR
323 in quiet cats are 132 ± 19.[18] Considering that under anaesthesia even lower values could
324 be regarded as normal, for this trial bradycardia was defined as HR lower than 100.
325 Regarding the systolic arterial pressure, according to Domanjko and colleagues normal
326 values range from 100 to 150 mmHg in anaesthetized cats.[19] Hence, in the present study
327 values higher than 150 mmHg were considered indicative of hypertension.
328 One limitation of the proposed anaesthetic protocol is that the addition of alfaxalone,
329 which is available on the market only at a concentration of 10 mg/ml, greatly increases
330 the volume of injectate in comparison to a classical dexmedetomidine-ketamine
331 combination. This certainly makes the intramuscular injection an unpleasant experience
332 for feline patients, and implies that two injections are often necessary to split the
333 volume into two anatomic sites. Additionally, a high volume IM injection carries the
334 potential for iatrogenic muscular injuries. In the light of these considerations, it was
335 decided to fix the maximal alfaxalone dose at 2.5 mg/kg (corresponding to a volume of

0.25 ml/kg). Nevertheless, none of the cats enrolled in the study showed signs of pain at the injection sites or impairment of the injected limb motor function in the post-anaesthetic period.

One important thing to consider when comparing different anaesthetic treatments is that the procedures to be performed in the anaesthetized patients should be similar in terms of duration and degree of nociceptive stimulation. Because of the clinical nature of the current trial, a standardization of the surgical procedure was not possible. After an attentive analysis of the caseload of the Institution in which the study was conducted, it was decided to enroll only cats undergoing one of the two most common minor procedures. Unarguably, the surgical curettage of a skin wound and the removal of a pin from a bone may be different in terms of types and intensity of nociceptive stimulation. However, the even distribution of the types of procedure, and the lack of significant difference in its duration, between treatments, should have prevented our findings from being biased.

Conclusions

The modified optimization method as described by Berenbaum was easy to apply and allowed to establish a useful drug combination to be used in clinical patients.

Dexmedetomidine-alfaxalone-butorphanol combination, at the doses of 0.014, 2.5 and 0.3 mg/kg, respectively, produces good quality injectable anaesthesia, characterized by

reliability, rapid onset and lack of complications, in feline patients and can be recommended for minor surgical procedures.

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Conflict of interest The authors do not have any potential conflicts of interest to declare.

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Figure legends

Figure 1

Box and whisker plots of duration of the clinical procedure in 120 anaesthetized cats. Boxes represent the interquartile range (central 50% of values), while the horizontal lines within the boxes are the medians. The upper and lower whiskers represent the upper and lower ranges of values, respectively. The dots represent the outliers.

Figure 2

Box and whisker plots of heart rates (beats per minute) of 120 cats undergoing minor surgical procedures under injectable anaesthesia. Boxes represent the interquartile range (central 50% of values), while the horizontal lines within the boxes are the medians. The upper and lower whiskers represent the upper and lower ranges of values, respectively. The dots represent the outliers.

Figure 3

Box and whisker plots of respiratory rates (breaths per minute) of 120 cats undergoing minor surgical procedures under injectable anaesthesia. Boxes represent the interquartile range (central 50% of values), while the horizontal lines within the boxes are the medians. The upper and lower whiskers represent the upper and lower ranges of values, respectively. The dots represent the outliers.

Figure 4

Box and whisker plots of systolic arterial pressures (mmHg) of 120 cats undergoing minor surgical procedures under injectable anaesthesia. Boxes represent the interquartile range (central 50% of values), while the horizontal lines within the boxes are the medians. The upper and lower whiskers represent the upper and lower ranges of values, respectively. The dots represent the outliers.