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# Effect of methadone and acepromazine premedication on tear production in dogs

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## ABSTRACT

**Objectives** To evaluate the combined effect of intramuscular acepromazine and methadone on tear production in dogs undergoing general anaesthesia for elective, non-ocular procedures.

**Design** Prospective, non-randomised, pre-post treatment study.

**Setting** Patients were recruited from a referral practice in the UK.

**Methods** Thirty client-owned dogs were enrolled in this study and received a combined intramuscular premedication of methadone (0.3 mg/kg) and acepromazine (0.02 mg/kg) before general anaesthesia for elective, non-ocular procedures. Full ophthalmic examination was performed and tear production was quantified using the Schirmer tear test-1 (STT-1). On the day of general anaesthesia, an STT-1 was performed before (STT-1a) and after (STT-1b) intramuscular premedication with methadone/acepromazine.

**Results** Using a general linear model, a significant effect on STT-1 results was found for premedication with methadone/acepromazine (P=0.013), but not eye laterality (P=0.527). Following premedication, there was a significant reduction observed in the mean STT-1 readings of left and right eyes between STT-1a (20.4±2.8 mm/min) and STT-1b (16.9±4.1 mm/min; P<0.001). Significantly more dogs had an STT-1 reading less than 15 mm/min in one or both eyes after premedication (30 per cent; 9/30 dogs) compared with before premedication (6.7 per cent; 2/30 dogs; P=0.042).

**Conclusions** An intramuscular premedication of methadone and acepromazine results in a decrease in tear production in dogs before elective general anaesthesia. This may contribute to the risk of ocular morbidities, such as corneal ulceration, particularly in patients with lower baseline tear production.

## INTRODUCTION

The precorneal tear film is composed of a lipid, aqueous and mucin layer, and is essential for the maintenance of ocular health.[1] It provides lubrication, mechanical removal of debris, immunological support and nutrition to the avascular cornea.[2] The tear film also provides an optically smooth surface, which contributes to refraction and therefore optical power of the eye.[1 3] The standard method of quantifying aqueous tear production in veterinary practice is the Schirmer tear test-1 (STT-1), which measures both reflex and basal tear production.[4 5]

Several studies have investigated the effects of commonly administered sedative drugs on tear production in dogs, as measured by the STT-1.[6–10] An opioid combined with a tranquiliser or sedative agent is commonly used as an analgesic and to allow reduction in doses of sedative and anaesthetic drugs.[11 12] There are inconsistent findings regarding the effect on tear production following the administration of full μ-opioid receptor agonists, either alone or in combination with sedative or tranquilising drugs. Significant reductions[6–8] and equivocal changes[9] on tear production have been observed. For example, in the clinical canine study by Dodam and others,[8] intramuscular acepromazine (0.03 mg/kg), a phenothiazine derivative, combined with oxymorphone (0.1 mg/kg), a full μ-opioid receptor agonist, resulted in a moderate decrease in STT-1 measurements from 21±2 mm/min at baseline to 15±2 mm/min postsedation (P<0.05). In contrast, Biricik and others[6] demonstrated marked reductions in tear production from 18.34±1.94 and 18.25±1.68 mm/min at baseline to 10.81±2.54 and 11.18±1.54 (P<0.001) in dogs administered only pethidine or fentanyl, respectively, both of which are also full μ-opioid receptor agonists, without the addition of a sedative drug.

Methadone, another full μ-opioid receptor agonist, is licensed in the UK as a premedication agent for dogs undergoing general anaesthesia. In combination with acepromazine, methadone provides sedation,[12 13] reduces the minimum alveolar concentration of isoflurane and causes less vomiting than acepromazine combined with morphine.[12] To date, its effects on tear production in dogs have not been evaluated.

The purpose of this study was to determine the combined effect of intramuscular acepromazine (0.02 mg/kg) and methadone (0.3 mg/kg) on STT-1 results in dogs before general anaesthesia for elective, non-ocular

surgeries. The null hypothesis was that there would be no effect of intramuscular acepromazine and methadone on STT-1 readings.

## METHODS

For this study informed owner consent was obtained. Thirty-eight client-owned dogs were recruited at a multidisciplinary small animal veterinary referral hospital in the UK.

Inclusion criteria required that all dogs be systemically well, unaffected by ocular disease that could affect STT-1 results and undergoing general anaesthesia for reasons unrelated to ocular health. An ophthalmic exam was performed on all patients by an ECVO board-certified ophthalmologist or resident. Ophthalmic examination included slit-lamp biomicroscopy (SL-14 Kowa, Optimed, California, USA), indirect ophthalmoscopy (Heine Omega 120, Germany and 2.2 Panretinal Volk lens, Ohio, USA) and tonometry (iCare Tonovet, Finland). Ophthalmic examination was performed after the STT-1 procedure to ensure no effect on STT-1 readings from either eyelid manipulations or photic stimulation. Dogs with an incipient cataract or minor fundic abnormality, such as inactive chorioretinal scarring, were included. Exclusion criteria included an initial baseline STT-1 of less than 10 mm/min, adnexal, ocular surface or intraocular disease with potential for modifying STT-1 results, patients on topical or systemic medication and any patient with an adverse reaction to the STT-1 procedure. Where investigators were available, dogs admitted the day before surgery had an additional STT-1 (STT-1h) performed within two hours of admission to the hospital on the day before premedication, to evaluate the effects of overnight hospitalisation on STT-1 results. No drugs were administered to these patients overnight. The remaining dogs were either hospitalised overnight without an STT-1h reading, or admitted on the day of their procedure.

All STTs were performed by the first author. Measurements were taken bilaterally starting with the left eye, followed by the right eye. A standardised 5 mm×35 mm strip of sterile Whatman no. 41 filter paper from a single batch (STT strips, Schering-Plough Animal Health, Uxbridge, Middlesex, UK) was folded at the notch within the sachet before placement. The strip was placed into the conjunctival fornix at the lateral third of the lower eyelid, ensuring contact with the corneal surface. Migration of tears via capillary action onto the strip was measured in millimetres at 60 seconds.

On the day of surgery, all dogs underwent two STT-1 tear tests: an initial baseline STT-1 (STT-1a) between 7:00 and 8:00 hours to minimise variation resulting from circadian rhythms, and a second STT-1 (STT-1b) after receiving a combined intramuscular premedication of acepromazine (0.02 mg/kg; PromAce, Boehringer Ingelheim Vetmedica, St Joseph, Missouri, USA) and methadone (0.3 mg/kg; Comfortan, Dechra Veterinary Products, Shropshire, UK), before general anaesthesia. STT-1b was performed between 8:30 and 14:00 hours. Timing of premedication, and therefore STT-1b measurement, was dependent on the daily hospital schedule. The times from premedication to STT-1b ('*premed to STT-1b*'), and from STT-1a to STT-1b ('*time between STT-1a and STT-1b*') were recorded (figure 1).

Sample size calculations indicated that a population of more than 12 dogs per group would give a statistical power of 0.9 with an alpha of 0.05 for detecting a change in mean STT-1 results of 5 mm after premedication, based on changes in STT-1 readings in dogs premedicated with medetomidine and butorphanol.[10] Data were analysed using Minitab 17 Statistical Software (Minitab, State College, Pennsylvania, USA). Deviations from assumptions of normality were assessed using graphical displays, including histograms and Q-Q plots, and the Anderson-Darling test. Parametric data are presented as mean (±SD) and non-parametric data are presented as median (range).

Data for STT-1 readings were measured on the left and right eyes. A general linear model was used to assess for dog identity and eye laterality as random effects and premedication as a fixed effect, with STT-1 measurement as the dependent variable. Eye laterality was nested within dog identity to account for lack of independence

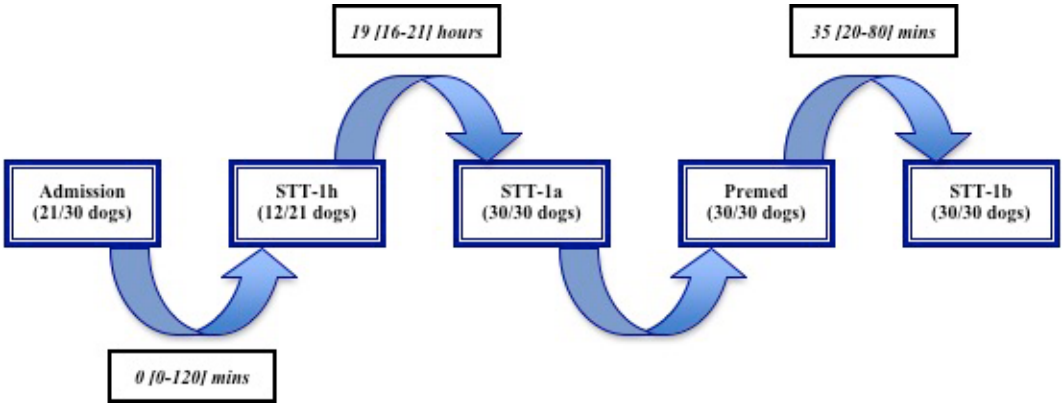


**Figure 1** Timeline of events illustrating admission to hospital, Schirmer tear test (STT)-1h, STT-1a, intramuscular premedication ('premed') with methadone (0.3mg/kg) and acepromazine (0.02 mg/kg) and STT-1b.

between these factors. An interaction term for dog identity with premedication was included in the model. A general linear model with a Tukey post hoc method was also used on any hospitalised dogs with STT-1h readings to evaluate changes in STT-1 readings, with input as above but adding measurement point (STT-1h, STT-1a or STT-1b) as a fixed effect. Times '*premed to STT-1b*' and '*time between STT-1a and STT-1b*' were not included as terms in these models as they were defined by dog identity and produced a multicollinearity error. Instead, in order to investigate potential effects of hospitalisation on mean (average between the left and right eye) STT-1 readings, Pearson's correlation was calculated to investigate whether mean STT-1b results were affected by either '*time between STT-1a and STT-1b*' or '*premed to STT-1b*' time. Statistical significance was set at P<0.05.

In order to assess the clinical relevance of any changes following premedication, the Fisher's exact test was used to compare proportions of dogs with at least one eye with an STT-1 reading less than a clinically defined cut-off value of 15 mm/min before and after premedication, and during hospitalisation.

## RESULTS

Of 38 recruited dogs, 8 dogs were excluded due to abnormal ophthalmic examination (n=4), baseline STT-1 result of less than 10 mm/min (n=2), distress during the STT-1 procedure (n=1) or additional systemic medication administered before premedication (n=1). Thirty dogs were included in the data analysis. Breeds and signalments were mixed and are outlined in table 1.

Of 30 dogs, 21 were hospitalised overnight before premedication, and 12 of those that were hospitalised were assessed for STT-1h (figure 1). The time between STT-1h and STT-1a was 19 (16–21) hours. The '*time between STT-1a and STT-1b*' was 110 (35–430) minutes and '*premed to STT-1b*' was 35 (20–80) minutes. Following premedication, there was a significant reduction observed in the mean STT-1 readings between STT-1a (20.4±2.8 mm/min) and STT-1b (16.9±4.1 mm/min; P<0.001, table 1, figure 2).

The general linear model indicated an effect on STT-1 reading of dog identity (P=0.008), premedication (P<0.001) and an interaction between dog with premedication (P=0.013), but not laterality of the eye (P=0.527). The adjusted $R^2$ for this model was 68.9 per cent.

Significantly more dogs had STT-1b readings of less than 15 mm/min in at least one eye (n=9/30; 30 per cent), compared with STT-1a (n=2/30; 6.7 per cent) (P=0.042). Of the nine dogs with STT-1b readings of less than 15 mm/min, seven were bilateral and breeds represented were mixed: French Bulldog (n=1), English Springer Spaniel (n=1), Labrador (n=2), crossbreed (n=2), Cavalier King Charles Spaniel (n=1), Tibetan Terrier (n=1) and Staffordshire Bull Terrier (n=1).

There was no statistically significant correlation between the change from '*mean STT-1a to STT-1b*' readings and the time from '*premed to STT-1b*' (P=0.771), or between the '*mean STT-1a to STT-1b*' and the '*time between STT-1a and STT-1b*' (P=0.050, figure 3).

To evaluate the effects of hospitalisation, further tests were performed on subgroups. There was no significant difference when comparing STT-1a readings using a 2-sample t-test for hospitalised (n=21/30) versus non-hospitalised (n=9/30) dogs (mean STT-1a: 19.9±2.88 mm/min; 21.5±2.29 mm/min, respectively; P=0.129). Separate general linear models similar to that described previously for all hospitalised dogs (n=21) and non-hospitalised dogs (n=9) both indicated an effect on STT-1 reading of premedication (P=0.001 and P=0.007, respectively) but not laterality of the eye (P=0.334 and P=0.972, respectively). The adjusted $R^2$ for these models was 69.1 per cent and 68.6 per cent, respectively.

For hospitalised dogs with an STT-1h reading (n=12/30), a general linear model indicated an effect on STT-1 reading of dog identity (P=0.018), and measurement point of STT-1 reading (STT-1h, STT-1a or STT-1b; P<0.001), but not the laterality of the eye (P=0.725). The adjusted $R^2$ for this model was 58.2 per cent. Coefficients for measurement points were significant for STT-1h (2.861; P<0.001) and STT-1b (−2.931; P<0.001) indicating that these time points were associated with significant changes in the average STT-1 measurement (0.069; P=0.895), but not STT-1a.

There was no statistical difference in the number of dogs with an STT-1 result less than 15 mm/min between STT-1h (n=0/12) and STT-1a (n=2/30; P=1), although both dogs with an STT-1a result of less than 15 mm/min were hospitalised overnight.

## DISCUSSION

The results of this study demonstrate a reduction in tear production, and an increased number of dogs with an STT-1 reading of less than 15 mm/min, after intramuscular administration of acepromazine (0.02 mg/kg) and methadone (0.3 mg/kg) in dogs undergoing elective anaesthesia. It is widely accepted that the STT-1 reading in clinically normal dogs should be greater than 15 mm/min.[4 14–18] While clinically normal dogs can have STT-1 readings of less than 15 mm/min without apparent ocular pathology, the reduction in tear production caused by the administration of a sedative and opioid may be sufficient to cause desiccation of the corneal surface and subsequent ulceration, particularly in dogs with a lower baseline STT-1 value or other predisposing factor.

To the authors' knowledge, the effects of acepromazine and methadone on tear production have not been reported, despite the frequency of use of this combination in clinical practice in the UK. Currently, there is conflict in the literature about the effects of full μ-agonist opioids on tear production. Mouney and others[9] found no significant changes in tear production following general anaesthesia in dogs administered either acepromazine (0.05 mg/kg) or morphine (1 mg/kg), a

**Table 1** Patient signalment; STT-1 results for left and right eyes (mm/min) for STT-1h, STT-1a and STT-1b; time (minutes) between premedication and STT-1b measurement

| | | | | STT-1h | | | STT-1a | | | STT-1b | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dog | Breed | Sex | Age | Left | Right | Mean | Left | Right | Mean | Left | Right | Mean | Premed-STT-1b* |
| 1 | Crossbreed>30 kg | MN | 1 y 6 m | 18 | 23 | 20.5 | 19 | 21 | 18 | 18 | 19 | 18.5 | 30 |
| 2 | French Bulldog | FN | 4 y 4 m | – | – | n/a | 24 | 23 | 23.5 | 13 | 13 | 13 | 30 |
| 3 | Labrador | ME | 5 y 5 m | – | – | n/a | 20 | 22 | 21 | 21 | 16 | 18.5 | 30 |
| 4 | Crossbreed 10–30 kg | FE | 6 y 3 m | – | – | n/a | 24 | 23 | 23.5 | 16 | 16 | 16 | 30 |
| 5 | English Springer Spaniel | MN | 4 y 5 m | 18 | 20 | 19 | 13 | 17 | 15 | 10 | 10 | 10 | 30 |
| 6 | Labrador | FE | 3 y 4 m | 21 | 22 | 21.5 | 19 | 20 | 19.5 | 22 | 17 | 19.5 | 30 |
| 7 | Doberman Pinscher | FN | 7 y 9 m | 30 | 26 | 28 | 21 | 19 | 20 | 16 | 20 | 18 | 35 |
| 8 | Labrador | ME | 1 y 11 m | – | – | n/a | 18 | 19 | 18.5 | 8 | 14 | 11 | 30 |
| 9 | Golden Retriever | FN | 6 y 1 m | 30 | 30 | 30 | 26 | 26 | 26 | 23 | 20 | 21.5 | 35 |
| 10 | Rottweiler | FN | 3 y 1 m | – | – | n/a | 24 | 25 | 24.5 | 21 | 21 | 20.5 | 80 |
| 11 | Jack Russell Terrier | FE | 6 m | 23 | 21 | 22 | 23 | 22 | 22.5 | 15 | 17 | 16 | 80 |
| 12 | Crossbreed>30 kg | MN | 2 y | 19 | 19 | 19 | 20 | 19 | 19.5 | 20 | 19 | 19.5 | 30 |
| 13 | Crossbreed 10–30 kg | MN | 7 y 7 m | – | – | n/a | 17 | 18 | 17.5 | 13 | 12 | 12.5 | 40 |
| 14 | Tibetan Terrier | MN | 9 y 3 m | – | – | n/a | 21 | 21 | 21 | 17 | 14 | 15.5 | 30 |
| 15 | Labrador | MN | 3 y 3 m | – | – | n/a | 19 | 16 | 17.5 | 14 | 11 | 12.5 | 45 |
| 16 | Labrador | ME | 10 y 4 m | – | – | n/a | 15 | 18 | 16.5 | 19 | 20 | 19.5 | 70 |
| 17 | Crossbreed 10–30 kg | FN | 5 y 3 m | 24 | 24 | 24 | 16 | 19 | 17.5 | 16 | 18 | 17 | 35 |
| 18 | Cairn Terrier | FN | 2 y 8 m | – | – | n/a | 24 | 25 | 24.5 | 23 | 24 | 23.5 | 45 |
| 19 | Golden Retriever | FN | 5 y 8 m | – | – | n/a | 26 | 22 | 24 | 23 | 26 | 24.5 | 30 |
| 20 | Lurcher X | FN | 5 y 2 m | 17 | 24 | 20.5 | 20 | 19 | 19.5 | 17 | 0 | 8.5 | 45 |
| 21 | Border Terrier | MN | 2 y 9 m | – | – | n/a | 24 | 22 | 23 | 17 | 18 | 17.5 | 20 |
| 22 | Cavalier King Charles Spaniel | FN | 6 y 1 m | – | – | n/a | 20 | 19 | 19.5 | 16 | 15 | 15.5 | 40 |
| 23 | Labrador | MN | 7 y 8 m | – | – | n/a | 19 | 20 | 19.5 | 18 | 17 | 17.5 | 40 |
| 24 | Labrador | ME | 6 m | – | – | n/a | 19 | 17 | 18 | 19 | 17 | 18 | 30 |
| 25 | Cockerpoo | FN | 3 y 6 m | – | – | n/a | 20 | 18 | 19 | 17 | 22 | 19.5 | 30 |
| 26 | Cavalier King Charles Spaniel | FE | 2 y 4 m | – | – | n/a | 23 | 20 | 21.5 | 9 | 13 | 11 | 30 |
| 27 | Labrador X | FN | 2 y 3 m | 20 | 30 | 25 | 22 | 22 | 22 | 20 | 20 | 20 | 45 |
| 28 | Staffordshire Bull Terrier | FN | 1 y 7 m | 17 | 20 | 18.5 | 14 | 17 | 15.5 | 10 | 14 | 12 | 35 |
| 29 | Crossbreed 10–30 kg | FN | 4 y 3 m | 24 | 24 | 24 | 23 | 20 | 21.5 | 23 | 21 | 22 | 35 |
| 30 | Labrador | FE | 8 m | – | – | n/a | 20 | 22 | 21 | 20 | 16 | 18 | 80 |
| **Total (mean±SD)** | | | | 23.6±3.6 | 21.8±4.6 | **22.7±3.7** | 20.4±2.5 | 20.4±3.3 | **20.4±2.8** | 16.6±4.9 | 17.1±4.2 | **16.9±4.1** | |

*Time between intramuscular premedication with methadone (0.3 mg/kg) and acepromazine (0.02 mg/kg) and STT-1b reading measured in minutes.
m, month; ME, entire male; MN, neutered male; FE, entire female; FN, neutered female; STT, Schirmer tear test; y, year.

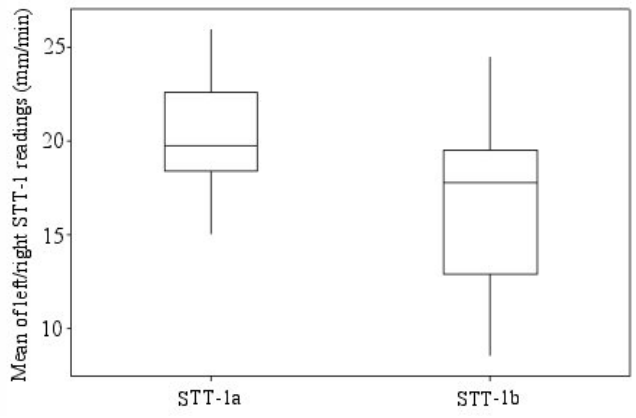


**Figure 2** Comparison of mean Schirmer tear test (STT)-1 results (mm/min) in 30 dogs before (STT-1a) and after (STT-1b) administration of acepromazine (0.02 mg/kg) and methadone (0.3 mg/kg). There was a significant decrease in STT-1 results after acepromazine/methadone administration. Box represents the IQR with median value and whiskers at the 10th and 90th percentiles (significance set at P<0.05).

full μ-opioid agonist. In contrast, fentanyl and pethidine, which are also full μ-opioid agonists, have been shown to reduce tear production as sole agents without the added effect of a sedative drug.[6] A retrospective study also identified transdermal fentanyl administration as a risk factor for development of corneal ulceration in dogs that have undergone general anaesthesia,[19] although STT-1 measurements were not performed. Both fentanyl and pethidine, unlike methadone and morphine, are selective serotonin reuptake inhibitors, which may increase vasoconstriction, and pethidine is also anticholinergic, which directly reduces lacrimation.[20 21] These factors may contribute to the more profound reduction in tear production seen with these drugs than with either morphine[9] or methadone, from the data. However, the results of this study are consistent with previous clinical

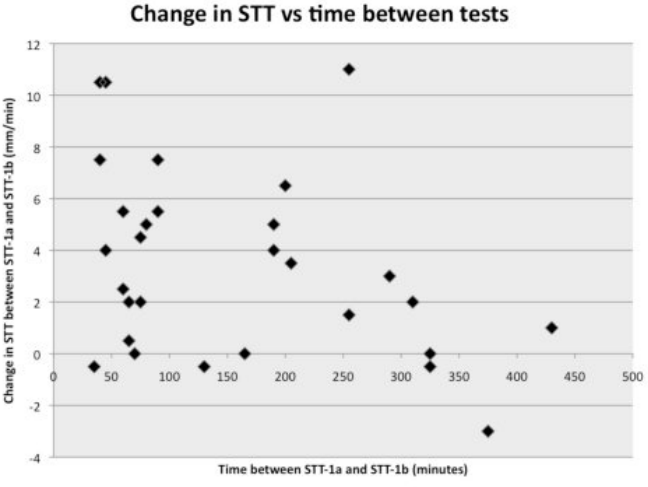


**Figure 3** Scatterplot of time between Schirmer tear test (STT)-1a and STT-1b (minutes) vs change in mean STT-1 result (mm/min). Results show no clear correlation between the variables.

studies that have demonstrated decreased tear production in dogs following administration of a full μ-opioid agonist combined with a sedative drug.[8 22] Both Dodam and others[8] and Ghaffari and others[22] demonstrated a greater decrease in STT-1 readings in dogs given combinations of xylazine/butorphanol or chlorpromazine/morphine, respectively, compared with each drug being administered separately. It is difficult to determine whether the decreased tear production seen in this study is the result of synergism of drug action between acepromazine and methadone or a single drug effect, however the authors speculate that synergism is present because combining acepromazine and methadone has been shown to provide more profound sedation than either drug administered individually.[12]

Dodam and others[8] proposed the following four mechanisms of action for the effect of sedatives/opioids on tear production: more effective antinociception, modification of central autonomic effect, reduced vascular supply to the tear glands caused by vasodilation or direct impact of the drugs on the glandular metabolism and local responses to stimuli. As neural control is the primary factor regulating tear production,[23] central nervous system depression caused by opioids may have the most significant impact on tear production.

Breeds that demonstrated an STT-1b reading of less than 15 mm/min were mixed and there was no clear breed predilection. Dogs were not excluded from this study on the basis of age. Hartley and others[24] demonstrated a decrease of 0.4 mm/year in STT-1 results obtained from a cross-sectional population dogs between 9 months and 11 years of age. A wide age range was represented in the study population, and in those patients with STT-1b results of less than 15 mm/min (52 (19–111) months). Diurnal variation was limited as much as possible, as previous studies have demonstrated circadian rhythms in canine tear production.[25 26] Hartley and others[24] demonstrated an increase of 0.7 mm when the STT-1 was performed a total of four times in one day between 10:00 and 16:00 hours. Similarly, Giannetto and others[25] also demonstrated a nocturnal acrophase in STT-1 values of normal Beagle dogs. Therefore, the STT-1 readings in the current study could have become affected by a slight increase due to the diurnal effect. Had this effect been taken into consideration, the lowering of STT-1 readings in association with administration of acepromazine/methadone may have been greater than reported here.

A limitation of this study is the lack of a control group to evaluate the effect of hospitalisation itself on the study population. Hospitalisation may affect tear production due to increased sympathetic drive in a hospital setting and subsequently decreased lacrimation, which is controlled by the parasympathetic nervous system. Chandler and others[27] demonstrated significantly reduced STT-1 results in clinically unwell dogs hospitalised in an intensive care unit, although the effects on STT-1 may have resulted from illness, drug effects or a direct result of the hospitalisation itself. In this study, STT-1h was

measured where possible to provide a true baseline STT-1 measurement on the dogs that were hospitalised overnight before premedication the following day because the authors felt that taking that a 'baseline' tear reading after a night of hospitalisation could be inaccurate. This population was not statistically powered because it was the secondary outcome of the study and not the primary objective for which data collection was ethically approved. Additionally, deriving statistical significance from this subpopulation was not possible without a pilot study and subsequent power calculation because, to the authors' knowledge, there are currently no peer-reviewed publications evaluating the effect of hospitalisation on clinically normal, non-medicated dogs on which to base a sample size calculation. While overnight hospitalisation in this study did significantly reduce tear production in the group of 12 hospitalised dogs with STT-1h readings, there were further reductions in STT-1 readings after acepromazine/methadone administration. In addition, there were significant reductions in STT-1 readings after acepromazine/methadone in both hospitalised and non-hospitalised groups. The authors did not find a significantly increased number of dogs with an STT-1 of less than 15 mm/min in one or both eyes after hospitalisation; however, this study may have lacked statistical power to separate the effect of hospitalisation alone. It should be noted that both dogs with an STT-1a reading of less than 15 mm/min had been hospitalised overnight before assessment. Additionally, lack of statistical power meant that the authors were unable to prove an association between change in STT-1 readings and *'time between STT-1a and STT-1b'* (figure 3), however the results did approach statistical significance. The authors are particularly interested in this hospitalisation effect, since it has not been thoroughly investigated or reported previously, and it warrants further clarification based on the results.

An additional limitation of this study is the time of 35 (20–80) minutes between premedication and subsequent measurement of STT-1b. Clinical studies by Bitti and others[13] and Monteiro and others[12] have demonstrated the onset of sedation following acepromazine/methadone administration within 15 min that lasts for over 120 min. The authors believe that tear production would likewise be affected for the duration of this period. It should be noted, however, that the degree of sedation achieved following the administration of acepromazine/methadone is variable. Future research could examine the effect of methadone on tear production, used either alone or in combination with other commonly used sedatives, alongside objective sedation scoring to qualify this further.

## CONCLUSION

When administered intramuscularly, the combination of acepromazine (0.02 mg/kg) and methadone (0.3 mg/kg) results in a decrease in tear production and reduces STT-1 results to less than 15 mm/min in at least one eye in 30 per cent of dogs undergoing elective general anaesthesia. Intramuscular combinations of acepromazine and methadone in dogs may add to the risk of ocular morbidities, such as corneal ulceration, in susceptible individuals.

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**Contributors** HAV, RLP, AP and DJG were involved in the study design. HAV was primarily involved with the acquisition of data and recruitment of subjects. EW was responsible for the statistical analysis and interpretation of data for the work. RLP, GVF and DJG were responsible for ophthalmic examination of subjects. All authors gave final approval of the version to be published.

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**Competing interests** None declared.

**Ethics approval** This study received institutional ethical approval from The Animal Health Trust Clinical Research Ethics Committee, Newmarket, UK (project number 23_2013, approved 24 September 2013).

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**Data sharing statement** There are no additional unpublished data.



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