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Naloxone reversal of an overdose of a novel, long-acting transdermal fentanyl solution in laboratory Beagles

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Opioid overdose in dogs is manifested by clinical signs such as excessive sedation, bradycardia, and hypothermia. The ability of two different intramuscular (i.m.) naloxone reversal regimens to reverse the opioid-induced effects of a fivefold overdose of long-acting transdermal fentanyl solution was evaluated in dogs. Twenty-four healthy Beagles were administered a single 13 mg/kg dose (fivefold overdose) of transdermal fentanyl solution and randomized to two naloxone reversal regimen treatment groups, hourly administration for 8 h of 40 (n = 8) or 160 μg/kg i.m. (n = 16). All dogs were sedated and had reduced body temperatures and heart rates (HRs) prior to naloxone administration. Both dosage regimens significantly reduced sedation ($P < 0.001$), and the 160 μg/kg naloxone regimen resulted in a nearly threefold lower odds of sedation than that of the 40 μg/kg i.m. naloxone regimen ($P < 0.05$). Additionally, naloxone significantly increased the mean body temperatures and HR ($P < 0.001$), although the 160 μg/kg regimen increased body temperature and HR more ($P < 0.05$). However, the narcotic side effects of fentanyl returned within 1–3 h following termination of the naloxone dosage regimens. The opioid-induced effects of an overdose of transdermal fentanyl solution can be safely and effectively reversed by either 40 or 160 μg/kg i.m. naloxone administered at hourly intervals.

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INTRODUCTION

The general recommendation for the selection and use of postoperative analgesics depends on the anticipated magnitude and duration of pain which in turn is influenced by the site, nature, and extent of surgery. In addition, both the characteristics of the analgesic and patient factors must be considered in the selection and continued use of an analgesic. The characteristics of an ideal analgesic have been considered and may include, in part, that the agent is a full agonist providing maximal analgesia for a wide range of pain states; has a rapid onset of action and a long duration of action; has linear kinetics; produces minimal adverse effects; is not vulnerable to important drug–drug interactions; is not significantly bound to plasma proteins; has no active metabolites; and it is reversible (Smith, 2008; Moore, 2009). Many strategies have been pursued to identify technologies that meet these characteristics. At the drug discovery level, attempts have been made to identify an ideal analgesic by engineering the mu-opioid receptor (Tao *et al.*, 2010). Others have concentrated on ways to alter existing analgesics or to combine existing analgesic compounds with drugs that may improve effectiveness while minimizing adverse effects (Smith, 2008).

Opioids have some features of ideal analgesics and are generally regarded as an important part of multimodal postoperative analgesia, especially for moderate-to-severe pain. In veterinary medicine, there are limited approved products and extended extra-label use of orally administered opioids in dogs beyond the immediate postoperative period is prevented by inherent limitations including poor oral bioavailability and rapid clearance (Pascoe, 2000). As a result, extra-label opioid use is primarily limited to preoperative epidural or intrathecal injections, single or repeat parenteral injections or constant rate intravenous infusions delivered during anesthesia. To overcome these limitations and prolong the therapeutic duration of action, other variations in opioid pharmaceutical delivery have been advanced for human or veterinary use that include extended release oral tablets (Holt *et al.*, 2007),

transdermal patches (Hofmeister & Egger, 2004), and liposome-encapsulated injectable opioids (Smith *et al.*, 2004). As a delivery method, the transdermal route has several potential strengths over oral and parenteral dose. These include noninvasive dosing, avoidance of the gastrointestinal tract, lack of first pass metabolism, steady, continuous drug delivery rather than a peak and trough phenomenon, potential reduction of side effects by elimination of peaks, possible reduction of lack of effectiveness owing to the elimination of troughs, and reduced dose frequency for convenience and increased compliance (Urquhart, 2000).

Recently, a novel, long-acting transdermal fentanyl solution (Recuvyra™ 50 mg/mL transdermal solution; Nexcyon Pharmaceuticals Ltd, London, UK) has been developed that potentially mitigates the disadvantages of oral, parenteral, and patch-delivered opioids and has several features of an ideal analgesic that include the following: fentanyl is a selective, μ-opioid receptor agonist with a potency 100 times that of morphine (Stanley, 1992); it has a rapid onset of action and long duration of action, providing analgesic concentrations of fentanyl within 2–4 h of application for a duration of at least 4 days (Freise *et al.*, 2012a,b); it has demonstrated dose-proportional plasma fentanyl concentrations following a single topical application (Freise *et al.*, 2012a); there are minimum adverse effects at the selected dose with well-known opioid adverse events increasing in magnitude and frequency when administered up to five times the dose (Savides *et al.*, 2012).

As an ideal drug feature, reversibility has not been examined with transdermal fentanyl solution. Reversibility allows clinicians to terminate the clinical effects of a drug when they are no longer deemed necessary to case management and permits intervention in the event of an overdose. Naloxone is an FDA approved opioid antagonist (NADA 035-825) that is considered the fentanyl reversal agent of choice in dogs because, as a pure opioid receptor competitive antagonist, it does not have the respiratory side effects of other opioid antagonists (Adams, 2001; Plumb, 2002). It has the highest affinity at the μ-opioid receptor and successfully reverses the effects of fentanyl citrate injections in the dog (Paddleford & Short, 1973; Veng-Pedersen *et al.*, 1995; Adams, 2001).

The outcome of a fivefold overdose of transdermal fentanyl solution has been described and includes, in part, moderate-to-severe sedation, reduced rectal temperature, and reduced HR (Savides *et al.*, 2012). It is likely that opioid-induced adverse events are reversible; however, given the long duration of action of transdermal fentanyl solution, it remains to be determined the duration of reversal from a single injection of naloxone. Therefore, the objective of this study was to determine an intramuscular (i.m.) naloxone reversal regimen to the opioid-induced effects from an overdose of transdermal fentanyl solution in dogs. To achieve the objective, two different i.m. naloxone doses were administered at hourly intervals and were evaluated for the reversal of peak sedation, reduced rectal temperature, and reduced HR in Beagle dogs following the administration of a single fivefold overdose (13 mg/kg) of transdermal fentanyl solution.

MATERIALS AND METHODS

Animals and experimental design

Twenty-four healthy (based on physical examination) purpose-bred laboratory Beagles (12 males/12 females), 5–6 months of age and ranging in bodyweight from 4.35 to 8.20 kg were selected. Dogs were individually housed, fed a commercial dry food formula and allowed *ad libitum* access to water. The animal facility temperature was maintained between 18 and 29 °C with 30–70% relative humidity. The 24 selected dogs were randomized to two different i.m. naloxone treatment groups, 40 μg/kg (n = 8) and 160 μg/kg (n = 16). An unbalanced study design was utilized because based on pilot experiments it was suspected that the recommended 40 μg/kg i.m. naloxone dose (Plumb, 2002) would not provide sufficient reversal at the administered dose of transdermal fentanyl solution. All dogs were administered a single fivefold (13.0 mg/kg) overdose (use dose of 2.6 mg/kg) of transdermal fentanyl solution (Recuvyra™ 50 mg/mL transdermal solution; Nexcyon Pharmaceuticals Ltd) to the ventral abdomen using a proprietary applicator tip as previously described (Freise *et al.*, 2012a). Prior studies demonstrated that plasma fentanyl concentrations were as high or higher with ventral abdomen application compared to the labeled dorsal, interscalpular region application (Freise *et al.*, 2012a). As this was an intentional overdose study, the worse case was examined with the ventral abdomen application. Sixteen hours after the application of transdermal fentanyl solution, when near maximal side effects were expected to be obtained (Savides *et al.*, 2012), i.m. naloxone was administered into the dorsal lumbar muscles hourly for eight doses according to the treatment randomization. Sedation assessments were conducted by blinded assessors as none or sedated. There was no attempt to distinguish mild, moderate, or severe sedation because a previous study with a fivefold transdermal fentanyl solution overdose demonstrated that all dogs were moderately or severely sedated (Savides *et al.*, 2012). In addition, the objective, continuous response variables of rectal body temperature and HR were collected 5 min before, 10 min after, and 40 min after each naloxone dose. Additional sedation, rectal temperature, and HR measurements were collected at −1, 0, 14, 15, 24, 26, and 28 h following transdermal fentanyl solution administration. Venous blood samples for plasma fentanyl and naloxone concentrations were also collected from each dog at 0 (prior to transdermal fentanyl solution administration), 16 (prior to the 1st naloxone administration), 20.083 (5 min following the 5th naloxone administration), and 24 (1 h following the last naloxone administration) hours post-transdermal fentanyl solution administration directly into sodium heparin blood collection tubes. Plasma was harvested by centrifugation at 1500 g for 10 min at 5 °C. Plasma samples were stored at −70 °C until analysis. All

procedures were approved by the local Institutional Animal Care and Use Committee.

Plasma sample analysis

Plasma fentanyl and naloxone concentrations were analyzed by liquid chromatography–tandem mass spectrometry. In brief, a stock solution of fentanyl (Cerilliant®, Round Rock, TX, USA) and a stock solution of naloxone (Cerilliant®) was diluted in 50:50 methanol (Honeywell Burdick & Jackson®, Morristown, NJ, USA):water (Milli-Q; Millipore Corp., Billerica, MA, USA) to a 25 and 250 μg/mL working solution, respectively. Control dog plasma (Bioreclamation Inc., Hicksville, NY, USA) was then serially diluted with the working solution to create standard curve samples ranging from 0.1 to 10 ng/mL of fentanyl and 1 to 1000 ng/mL naloxone. Additionally, an internal standard (IS) working solution of fentanyl-d_5 (Cerilliant®) and naltrexone (Cerilliant®) at concentrations 200 and 2000 ng/mL, respectively, was prepared in 50:50 methanol/water. A 100 μL each of sample, standard, quality control, or control blank was aliquoted directly into a 96-well block, and 20 μL of the IS working solution was added to all wells except for the control blanks, which instead had 20 μL of 50:50 methanol/water were added and vortexed. Four hundred microliter of 5% acetic acid (Mallinckrodt Baker, Phillipsburg, NJ, USA) in water was then added to each well, and the samples were vortexed again followed by centrifugation at 4 °C. Solid-phase extraction (SPE) then proceeded using Bond Elut® 96 Certify, 50 mg sample extraction blocks (Varian Corp., Palo Alto, CA, USA), and a Tomtec Quadra-96 Model 320 (Tomtech, Hamden, CT, USA). Sample blocks were conditioned twice with 400 μL of methanol, followed by equilibration with two 400-μL volumes of Milli-Q water and equilibration with two 400-μL volumes of 5% acetic acid in water. Samples were then transferred to the SPE block and slowly aspirated. The SPE block was then washed twice with 400 μL of 5% acetic acid in water followed by a two washes of 400 μL of methanol. Samples were slowly eluted from the SPE block with two 300-μL volumes of 2% ammonium hydroxide (EMD Biosciences, Darmstadt, Germany) in acetonitrile (Honeywell Burdick & Jackson®) and evaporated to dryness before reconstitution with 200 μL of 1% formic acid (EMD Biosciences) in acetonitrile.

Reconstituted samples were quantified using an API 3000 triple quadrupole mass spectrometer (Applied BioSystems/MDS SCIEX, Foster City, CA, USA) with peak area integration conducted using Analyst Software v 1.4 (Applied BioSystems/MDS SCIEX) data acquisition system. HPLC separation was achieved using a Thermo Betasil Silica-100 column (50 × 3 mm, 5 μm) (Thermo Fisher Scientific, Waltham, MA, USA) with the flow rate set at 0.5 mL/min. Mobile phase A consisted of 1% formic acid in water and mobile phase B consisted of 1% formic acid in acetonitrile. The mobile phase gradient started at 90% mobile phase B from 0.0 to 1.0 min, switched from 90% to 70% mobile phase B from 1.0 to 1.5 min, and switched back from 70% to 90% mobile phase B at 2.5 min. The injection volume was 10 μL, and mass spectrometer detection was conducted using positive ionization mode and monitoring of the transitions 337.2 $m/z \rightarrow$ 188.3 m/z for fentanyl, 342.2 $m/z \rightarrow$ 188.3 m/z for the IS fentanyl-d_5, m/z 328.2 $\rightarrow$ m/z 310.2 for naloxone, and m/z 342.2 $\rightarrow$ m/z 324.2 for the IS naltrexone. Standard curves were determined using linear and quadratic regression for fentanyl and naloxone, respectively, with $1/x^2$ weighting using Watson v7.0.0.01 (Thermo Fisher Scientific), where x is the nominal sample concentration. Typical squared correlation coefficient (R^2) values were 0.9972 and 0.9964 for fentanyl and naloxone, respectively. Concentration calculations were based on the peak area ratios of fentanyl to fentanyl-d_5 and of naloxone to naltrexone for fentanyl and naloxone, respectively. The intra- and inter-assay precision (i.e., coefficient of variation) was $\leq$ 8.6%, and the accuracy (i.e., relative error) ranged from −4.2% to 6.0% for both analytes. The lower limit of quantification (LLOQ) was 0.1 and 1.0 ng/mL for plasma fentanyl and naloxone, respectively.

Statistical methods

The sedation assessments were analyzed using a generalized linear repeated measures mixed effects model. The logit transformation of the mean probability of sedation, μ_i, for the ith subject was linearly related to time as follows:

$$\text{logit}(\mu_i) \equiv \log\left(\frac{\mu_i}{1-\mu_i}\right) = \begin{cases} \beta_B + b_i & \text{if } t \leq 0 \\ \beta_B + \beta_F + b_i & \text{if } 0 < t \leq 16 \\ \beta_B + \beta_F + \beta_N^{40} + b_i & \text{if } 16 < t \leq 24 \text{ and Dose} = 40\,\mu\text{g/kg} \\ \beta_B + \beta_F + \beta_N^{160} + b_i & \text{if } 16 < t \leq 24 \text{ and Dose} = 160\,\mu\text{g/kg} \\ \beta_B + \beta_F + b_i & \text{if } t > 24 \end{cases}$$

where t is the nominal time of observation in hours, β_B, β_F, β_N^{40}, and β_N^{160}, are the baseline, fentanyl, 40 μg/kg i.m. naloxone, and 160 μg/kg i.m. naloxone fixed effect terms, respectively. Additionally, b_i is the subject-specific random effect term that is normally distributed with mean 0 and variance σ^2. The overall narcotic reversal effect of i.m. naloxone administered at hourly intervals on sedation was tested with the null hypothesis of $\frac{1}{3}\cdot\beta_N^{40} + \frac{2}{3}\cdot\beta_N^{160} \geq 0$ vs. the alternative hypothesis $\frac{1}{3}\cdot\beta_N^{40} + \frac{2}{3}\cdot\beta_N^{160} < 0$. The unequal weighting of β_N^{40} and β_N^{160} was used to account for the unbalanced design of the study (n = 8 and n = 16 for the 40 and 160 μg/kg naloxone doses, respectively). The narcotic reversal effectiveness of each naloxone dose was tested with the null hypotheses that $\beta_N^{40} \geq 0$, $\beta_N^{160} \geq 0$ vs. the alternative hypotheses that $\beta_N^{40} < 0$, $\beta_N^{160} < 0$. To test the additional effect of 160 μg/kg vs. a 40 μg/kg i.m. naloxone doses administered at hourly intervals, the null hypothesis of $\beta_N^{160} \geq \beta_N^{40}$ was tested against the alternative hypothesis that $\beta_N^{160} < \beta_N^{40}$. As 100% of dogs in both group 1 and 2 were sedated during the time intervals $0 < t \leq 16$ and $t > 24$, a large correlation (near −1.00) existed between β_F and β_N^{40}, β_N^{160}, resulting in large standard errors of the parameters estimates. The large degree of correlation results in many combinations of

parameter estimates giving almost identical fits to the data. To alleviate this issue, the β_F parameter was fixed to the initially estimated value (i.e., the estimate when all five terms in the model were simultaneously estimated), and then, the statistical analysis was conducted to determine the effect of naloxone on sedation, conditional on the fixed value of β_F. The β_F parameter was chosen to be fixed as it is already known that fentanyl has sedative effects (Freise *et al.*, 2012b; Adams, 2001; Plumb, 2002) and because the interest of the study was the effect of naloxone, not the effect of fentanyl. A sensitivity analysis was subsequently conducted to determine the effect on the statistical conclusions of changing the value of β_F to other reasonable values.

The body temperature and HR were analyzed with a linear repeated measures mixed effects model with dose, nominal time, and dose by nominal time interaction terms as fixed effects and subject as a random effect in the model. The covariance structure in the repeated measures analysis was investigated using three structural assumptions, namely compound symmetry, first-order autoregressive, and heterogeneous first-order autoregressive. The assumption that gave the minimum value of the Akaike's Information Criterion was selected for the final model (Akaike, 1974). For both body temperature and HR, the first-order autoregressive model was selected. The overall narcotic reversal effect of i.m. naloxone administered at hourly intervals was tested with a null hypothesis of $\mu_N \leq \mu_F$, vs. the alternative hypothesis $\mu_N > \mu_F$, where μ_N is the mean body temperature or HR during the naloxone treatment time period ($16 < t \leq 24$) and μ_F is the mean body temperature or HR during the fentanyl only time period ($t = 14, 15, 15.917, 26, 28$). To test the additional effect of 160 μg/kg vs. a 40 μg/kg i.m. naloxone doses administered at hourly intervals, the null hypothesis of $\mu_N^{160} \leq \mu_N^{40}$ was tested against the alternative hypothesis of $\mu_N^{160} > \mu_N^{40}$, where μ_N^{40} and μ_N^{160} are the mean body temperatures or HRs during the naloxone treatment time period for the 40 and 160 μg/kg i.m. naloxone dose groups, respectively.

All statistical analyses and calculations were conducted in SAS (version 9.1.3 Service Pack 4; SAS Institute Inc., Cary, NC, USA). The sedation scores were analyzed using the NLMIXED procedure, and the body temperatures and HR were analyzed using the MIXED procedure. Statistically significant differences were determined at the $\alpha = 0.05$ probability of a type I experiment-wise error. To control the experiment-wise error rate, the unadjusted *P*-values were corrected using the step-down Bonferonni method for multiple tests on each response variable (Holm, 1979). Specific hypotheses were tested using the ESTIMATE statement in SAS and unadjusted *P*-values constructed using a Student's *t*-test.

RESULTS

The plasma naloxone and fentanyl concentrations are displayed in Table 1. Plasma fentanyl concentrations were below the LLOQ prior to dosing in all dogs, and the mean fentanyl concentrations ranged from 4.60 to 6.53 ng/mL across both groups from 16 through 24 h following the administration of a fivefold overdose (13 mg/kg) of transdermal fentanyl solution. The plasma naloxone concentrations were also below the LLOQ prior to i.m. naloxone dose administration in all dogs. At 5 min following the 5th naloxone dose administration (20.083 h), the plasma naloxone concentrations were 10.4 ± 0.238 (mean ± standard error) and 34.7 ± 1.76 ng/mL in the 40 and 160 μg/kg i.m. naloxone dose groups, respectively. At 24 h, the mean plasma naloxone concentrations had dropped substantially from the previous peaks in both groups, consistent with its known short duration of action and rapid clearance (Veng-Pedersen *et al.*, 1995; Adams, 2001; Plumb, 2002). No seizures or other adverse affects of naloxone administration were observed in any dogs.

The observed proportions of dogs sedated vs. time are displayed in Fig. 1 for both the 40 and 160 μg/kg naloxone dose groups. As can be observed, the baseline, pretransdermal fentanyl solution administration proportion of sedated dogs is near 0.0. For nonapparent reasons, six dogs were scored as sedated at the time of transdermal fentanyl solution application resulting in the proportion of sedated dogs being 0.4 and 0.2 in the 40 and 160 μg/kg groups, respectively, at time 0. Following a fivefold overdose of transdermal fentanyl solution, all dogs were sedated prior to naloxone administration (i.e., at 14, 15, 15.917 h). The administration of either 40 or 160 μg/kg i.m. naloxone at hourly intervals reduced the proportion of sedated dogs. The mean proportion of sedated dogs from 16 through 24 h for the 40 and 160 μg/kg dose groups was 0.698 and 0.438, respectively. Additionally, all dogs were determined to be sedated at least once from 16 through 24 h in both groups. The mean proportion of sedated dogs returned to 1.0 following cessation of the hourly i.m. naloxone administrations for both groups by 26 h.

Table 1. Plasma fentanyl and naloxone concentrations by treatment group

	Plasma fentanyl conc. (ng/mL)				Plasma naloxone conc. (ng/mL)			
	40 μg/kg i.m. naloxone		160 μg/kg i.m. naloxone		40 μg/kg i.m. naloxone		160 μg/kg i.m. naloxone	
Time (h)	Mean	Standard error	Mean	Standard error	Mean	Standard error	Mean	Standard error
0	<LLOQ	–	<LLOQ	–	<LLOQ	–	<LLOQ	–
16	4.60	0.537	5.46	0.295	<LLOQ	–	<LLOQ	–
20.083	5.92	0.873	5.80	0.358	10.4	0.238	34.7	1.76
24	5.42	0.919	6.53	0.568	2.78	0.201	12.8	0.848

<LLOQ, Less than lower limit of quantification for all subjects.

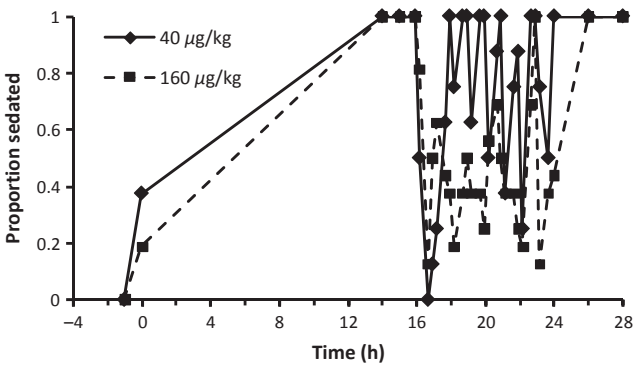

Fig. 1. Observed proportion of dogs sedated vs. time by i.m. naloxone treatment group.

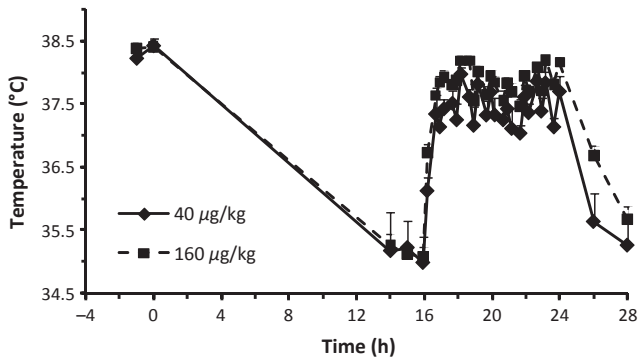

Fig. 2. Mean rectal body temperature vs. time by i.m. naloxone treatment group. Bars represent the standard error.

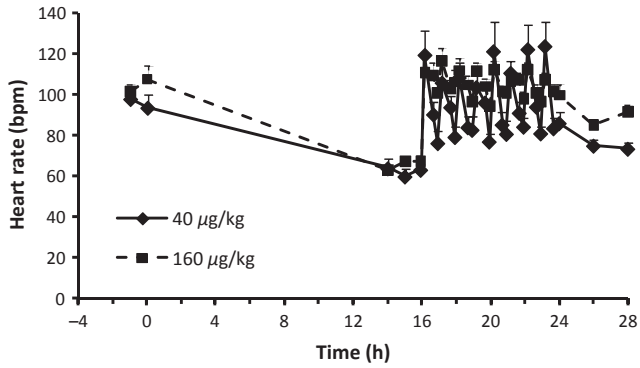

Fig. 3. Mean heart rate vs. time by i.m. naloxone treatment group. Bars represent the standard error.

The overall effect of naloxone on reversal of the sedative effects of transdermal fentanyl solution was statistically significant ($P < 0.001$), as was the individual effect of the 40 and 160 μg/kg i.m. naloxone reversal regimens ($P < 0.001$ for both regimens). The analysis also indicated that there was significant subject-to-subject variability in the sedation response (i.e., the probability that $\sigma^2 > 0$ was < 0.05). Furthermore, the reversal affect of the 160 μg/kg i.m. naloxone dose was significantly greater than that for the 40 μg/kg i.m. naloxone dose ($P = 0.0132$). The odds of a subject being sedated with a 160 μg/kg i.m. naloxone dose was 0.353 (95% confidence interval [0.0327–0.674]) fold that of a 40 μg/kg i.m. naloxone dose. Owing to the high degree of correlation (near −1.00) between β_F and β_N^{40}, β_N^{160}, the value of β_F was fixed to the initial estimate of 11.5. Varying the fixed value of β_F from 1 to 30 had no affect on the hypothesis test results (accurate numerical integration of the likelihood could not be achieved for values of $\beta_F > 30$), indicating that the results are robust to different reasonable fixed values of β_F.

The mean rectal body temperatures vs. time by i.m. naloxone dose group are displayed in Fig. 2. The rectal body temperatures across both groups dropped from 38.4 ± 0.0976 °C prior to transdermal fentanyl solution administration to 35.1 ± 0.0884 °C following transdermal fentanyl solution treatment (i.e., at time 14, 15, and 15.917 h). During i.m. naloxone reversal (i.e., from 16 through 24 h), the body temperature across both groups was 37.7 ± 0.0578 °C. By 26 and 28 h the body temperatures returned to near prenaloxone administration values with an overall mean of 35.9 ± 0.0976 °C. The mean body temperature during naloxone treatment time period (μ_N) was 2.19 ± 0.0638 °C higher than the mean during the fentanyl only time period (μ_F) ($P < 0.001$). Additionally, during the naloxone treatment time period, the body temperature was 0.412 ± 0.123 °C higher in the 160 μg/kg i.m. naloxone dose group (37.8 ± 0.0708 °C) than in the 40 μg/kg i.m. naloxone dose group (37.4 ± 0.100 °C, $P < 0.001$), indicating greater narcotic reversal effect of the higher i.m. naloxone dose.

The mean HRs vs. time by i.m. naloxone dose group are displayed in Fig. 3. The HRs across both groups dropped from 101 ± 3.31 bpm prior to transdermal fentanyl solution administration to 64.2 ± 3.04 bpm following transdermal fentanyl solution administration (i.e., at time 14, 15, and 15.917 h). During i.m. naloxone reversal (i.e., from 16 through 24 h), the HR across both groups returned to the prefentanyl administration HR with a value of 101 ± 2.41 bpm and then dropped again to an overall mean of 83.1 ± 3.31 bpm following termination of naloxone administration. The mean HR during naloxone treatment time period (μ_N) was 28.9 ± 1.78 bpm higher than the mean during the fentanyl only time period (μ_F) ($P < 0.001$). Finally, during the naloxone treatment time period, the HR was 9.97 ± 5.11 bpm higher in the 160 μg/kg i.m. naloxone dose group (104 ± 2.95 bpm) than in the 40 μg/kg i.m. naloxone dose group (94.4 ± 4.17 bpm, $P = 0.0258$), further indicating greater narcotic reversal effect of the 160 μg/kg i.m. naloxone dosage.

DISCUSSION

This study demonstrates that the opioid-induced effects of up to a fivefold overdose of transdermal fentanyl solution in dogs can be successfully reversed through administrations of either 40 or 160 μg/kg i.m. naloxone. Naloxone is an approved opioid antagonist for use in the dog where the recommended initial dose

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