Investigation of the effects of orally administered trazodone on intraocular pressure, pupil diameter, physical examination variables, and sedation level in healthy equids

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OBJECTIVE
To investigate the effects of orally administered trazodone on intraocular pressure (IOP), pupil diameter measured in the vertical plane (ie, vertical pupil diameter [VPD]), selected physical examination variables, and sedation level in healthy equids.

ANIMALS
7 horses and 1 pony.

PROCEDURES
Food was withheld for 12 hours prior to drug administration. After baseline (time 0) sedation scoring, physical examination, and measurement of IOP and VPD, equids received 1 dose (approx 6 mg/kg) of trazodone orally. Examination and measurement procedures were repeated 0.5, 1, 2, 4, 8, 12, and 24 hours after drug administration. Blood samples were collected at each time point for analysis of plasma trazodone concentrations. Repeated-measures analysis was used to compare examination results between downstream time points and baseline.

RESULTS
7 of 8 equids had mild sedation from 0.5 to 8 hours after treatment; compared with baseline values, mean IOP was significantly lower from 0.5 hours to 8 hours, mean VPD was significantly smaller at 0.5 hours, and mean rectal temperature was significantly lower from 1 to 8 hours after drug administration. Adverse effects (signs of excitement in 1 equid and sweating in 4) were self-limiting and considered minor. Mean maximum plasma concentration of trazodone was 1,493 ng/mL 0.75 hours after administration, and terminal half-life of the drug was 9.96 hours.

CONCLUSIONS AND CLINICAL RELEVANCE
The described oral dose of trazadone elicited sedation with a few self-limiting adverse effects in the study sample. Drug effects on IOP and VPD may alter ocular examination findings. Further investigation is warranted prior to use of trazodone for sedation in equids, particularly those with ophthalmic conditions. (*Am J Vet Res* 2021;82:138–143)

Trazodone is a serotonin antagonist and reuptake inhibitor most frequently prescribed in human medicine to treat insomnia.[1] In dogs, trazodone is used for long-term treatment of anxiety disorders and to facilitate activity restriction. Trazodone is shown to facilitate cage rest of dogs after orthopedic surgery because of the drug's calming effect.[2,3] Trazodone is also increasingly being used as an orally administered sedative for horses. Similar to dogs, equids restricted to stall rest for medical treatments may have undesirable behaviors as a result of anxiety, stress, and boredom. Recently, 2 studies[4,5] have evaluated the pharmacokinetics and pharmacodynamics of trazodone in horses; in one investigation, trazodone hydrochloride powder was administered IV at 1.5 mg/kg and orally at 4 mg/kg, and in the other investigation, commercially available 100-mg trazodone hydrochloride tablets were administered orally as suspensions in water at 7.5 and 10 mg/kg. Although the investigators of 1 study[4] reported signs of aggression (including pinning the ears back, kicking, and attempting to bite) after IV administration at the highest dose tested (2 mg/kg) during preliminary experiments, results of both studies[4,5] indicated that orally administered trazodone was rapidly absorbed and elicited desired sedative effects without major adverse effects.

Trazodone and other psychotropic drugs with similar receptor affinities have been previously associated with adverse ocular effects in people and nonhuman animals, and these findings may have implications for its use when monitoring and treating ophthalmic disease.[6] Low-dose oral administration of trazodone resulted in significantly increased IOP in a human patient with a history of angle-closure glau-

ABBREVIATIONS

C_{max}	Maximum plasma concentration
IOP	Intraocular pressure
VPD	Vertical pupil diameter

coma who had previously maintained IOP within the expected range for a healthy individual.[7] A study[8] of the effects of various topically applied medications in healthy rabbits found that ocular instillation of trazodone reduced IOP of the treated eye. However, to the authors' knowledge, there is no published literature describing the effects of trazodone on ocular variables in equids.

The objectives of the study reported here were to determine the effects of trazodone hydrochloride on IOP and VPD in equids after oral administration of a single dose prepared from commercially available tablets and to evaluate selected physiologic variables and sedative effects in treated equids. Our hypothesis was that oral administration of trazodone would cause transient reductions in IOP and VPD. A secondary aim of this study was to provide pharmacokinetic information for trazodone in this species after administration as described.

Materials and Methods

Animals

A convenience sample of 8 client-owned healthy adult equids was included in the prospective study. None of the included animals had prior known stereotypic behaviors, such as cribbing, stall pacing, or other repetitive behaviors. An a priori power analysis for a 2-sample *t* test ($\alpha = 0.05$) with an expected IOP difference of 5 ± 2 mm Hg between the treated and untreated condition indicated that a sample size of 6 was required to achieve a power of 80%. Eight equids were included in the study in anticipation of variation among individual animals and to increase power. All equids were deemed healthy on the basis of results of a physical examination, CBC, serum biochemical analysis, and complete ophthalmic examination, including slit-lamp biomicroscopy, direct and indirect ophthalmoscopy, and rebound tonometry. They were kept in a familiar environment and acclimated to IOP and VPD measurement procedures by taking measurements at 6-hour intervals for 48 hours prior to data collection. Food was withheld for 12 hours before to 12 hours after trazadone administration, and access to water was provided at all times. Informed consent was obtained for all animals prior to inclusion in the study. The study was approved by the Colorado State University Institutional Animal Care and Use Committee (protocol No. 19-9011A).

IV catheter placement and drug administration

The morning of trazodone administration, a site over the left jugular vein was aseptically prepared with betadine solution and alcohol. A local anesthetic block was performed with 2% lidocaine injectable solution[a] (0.5 mL, SC), and a 14-gauge, 5.25-inch IV catheter[b] was placed. The catheter was secured in place with 2-0 nylon suture and used to collect blood samples for measurement of plasma trazodone concentrations; for safety reasons, the catheter was removed 12 hours after trazodone administration, and the last blood sample (obtained 24 hours after drug administration) was collected from the left jugular vein via direct venipuncture.

The body weight of each equid was estimated with the following equation:

$$\text{Weight (kg)} = (\text{girth}^2\ [\text{cm}] \cdot \text{length}\ [\text{cm}])/11{,}877\ (\text{cm}^3/\text{kg})$$

with girth measured just behind the point of the elbow joint and length measured from the point of the shoulder joint to the tuber ischium.[9] A soft tape was used to obtain measurements. Body weight was not directly measured because a weight scale was not available. A dose of 6 mg/kg was calculated and rounded to the nearest complete tablet for administration. Trazodone hydrochloride tablets (50 mg)[c] were ground to powder with a mortar and pestle. The powder was reconstituted with 30 mL of tap water in a 60-mL catheter-tip syringe, and approximately 5 mL of corn syrup was added to the suspension to increase viscosity and palatability. The mixture was administered orally by syringe, and the equid's head was kept elevated for approximately 10 seconds to maximize success of administration.

Data collection

Baseline data were collected prior to drug administration. Before physical examinations, sedation was subjectively scored (0 = none, 1 = mild, 2 = moderate, and 3 = deep).[5] Scores were individually assigned by 2 examiners (ALM and RH) who were not blinded to treatment status while the horses were standing free in stalls. A consensus score was used for analyses. The noise stimulus used as part of the evaluation was a handclap performed outside the horse's vision field. The baseline scores were recorded and used for comparison with responses at predetermined time points after drug administration.

Head height from the ground was measured with a tape measure after subjective scoring was complete. Then, physical examination variables including heart rate (determined by cardiac auscultation), respiratory rate (determined by observing flank excursions), rectal temperature, and gastrointestinal motility (determined by auscultation of borborygmi in the upper and lower flank for 15 seconds on the right and left sides, with the degree of motility of the 4 quadrants annotated) were recorded.

A complete ophthalmic examination was performed by 1 observer (KLW) as previously described. Measurement of IOP was performed with rebound tonometry.[d] The equid's head was maintained in a neutral position at the level of the heart for each tonometry reading. Six consecutive measurements per eye were performed, and the final reading was determined by the tonometer as the mean of 4 measurements excluding the highest and lowest values. Measurement of pupil diameter in the vertical plane (ie, VPD) was then performed by 1 observer (ALM) for each eye with a flexible ruler[e] held close to the eye, immediately temporal to the

corpora nigra. Light intensity was maintained with a stable indoor environment, with minimal ambient light from the outside. Each equid was kept in the same stall for the duration of the study to reduce variability among measurements. The pupils were visually examined with an indirect light source held approximately 40 cm away from each eye and out of the direct line of sight.

After baseline data were collected, trazodone was administered as described. Data were collected in the same manner described for the baseline examinations 0.5, 1, 2, 4, 8, 12, and 24 hours after drug administration. Food was provided again after data collection at the 12-hour time point. Gastrointestinal motility after drug administration was scored as an unchanged (0), reduced (1), or increased (2) number of borborygmi from baseline. Equids were also evaluated for signs of additional drug effects at the same time points (eg, sweating or behavioral changes other than sedation), and these signs were recorded if present.

Blood samples were obtained at the same time points for measurement of plasma trazodone concentrations after all examinations were complete. For sample collection via the IV catheter, 12 mL of blood was withdrawn from the IV catheter and discarded prior to collection of 6 mL of blood into a sodium heparin–containing tube. The catheter was flushed with sterile heparinized saline (0.9% NaCl) solution after each collection. Samples were stored on ice before centrifugation at 1,400 × *g* for 5 minutes to seperate plasma, which was frozen at –20°C until analysis.

Drug concentration measurement and pharmacokinetic analysis

Trazodone concentrations were quantitated in plasma by use of a previously validated liquid chromatography–tandem mass spectrometry method as described elsewhere.[4,f–h] The response for trazodone on analytic assay was linear and yielded correlation coefficients of $R \geq 0.99$. Accuracy (percentage nominal concentration) was 95%, 100%, and 97% for trazodone concentrations of 0.3, 400, and 3,000 ng/mL, respectively. Precision (percentage relative SD) was 7%, 2%, and 2% for trazodone concentrations of 0.3, 400, and 3,000 ng/mL, respectively. The technique was optimized to provide a limit of quantitation of 0.1 ng/mL and a limit of detection of approximately 0.05 ng/mL for trazodone in plasma.

Pharmacokinetic analysis was performed by noncompartmental analysis with commercially available software.[i] The area under the plasma concentration-versus-time curve was calculated with the log-linear trapezoidal rule and extrapolation to infinity by dividing the last measured serum concentration by the terminal slope of the plasma concentration-versus-time curve (λ_z). The terminal half-life of trazodone was calculated with the formula $0.693/\lambda_z$.

Statistical analysis

Analysis was performed with commercially available software.[j] Residual diagnostic plots were used to evaluate model assumptions of normality and equal variance. For each equid, data collected at each time point after trazodone administration were compared with the baseline value for the same variable. For rectal temperature, heart rate, and respiratory rate, a mixed model was fit separately for each response variable. Time (0 [ie, baseline] and 0.5, 1, 2, 4, 8, 12, and 24 hours after drug administration) was included as a fixed effect. Equid was included as a random effect to account for repeated measures. When results of mixed-model analysis were significant, the Dunnett test was used to compare values at downstream time points with the baseline values. For IOP and VPD (for which measurements were obtained from both eyes), a similar model was used, but eye was also included as a random effect. For comparison of sedation scores, the Wilcoxon signed rank test was used. The Bonferroni method was used to account for multiple comparisons. Values of $P < 0.05$ were considered significant.

Results

Equids

The 8 equids included 3 American Quarter Horses, 2 Mustangs, 1 Thoroughbred, 1 mixed-breed horse, and 1 Connemara Pony. There were 4 mares and 4 geldings; the median age of the animals was 9.5 years (range, 4 to 17 years) and median body weight (as estimated by the measuring tape method) was 567 kg (range, 396 to 687 kg).

Sedation, physical examination, and ophthalmic assessments

At baseline, the sedation score was 0 of 3 (no sedation) for all equids. After oral administration of trazodone, 7 of 8 equids appeared mildly sedated (score of 1; lower ear and neck carriage compared with that observed before treatment, slightly delayed response to noise stimulus, or both) at all time points from 0.5 to 8 hours. Twelve hours after drug administration, 4 equids were assessed as mildly sedated and 4 had no signs of sedation. All sedation scores had returned to the baseline value by the 24-hour time point. One equid remained bright and alert (sedation score of 0) and showed signs of excitement (circling, with apparent hyperesthesia noted on the basis of increased responsiveness when touched) from 0.5 to 12 hours after drug administration. Twelve hours after drug administration, evidence of mild sedation was observed in this horse. However, there was no significant difference in the median sedation score, compared with that at baseline, at any time point **(Table 1)**. Four equids had moderate sweating over the entire body, including 1 with profound sweating to the point of agitation despite other signs consistent with mild sedation. Sweating resolved ≤ 4 hours after drug administration in all equids. No significant differences in heart rate or respiratory rate were detected after drug administration. Gastrointestinal mo-

Table 1—Comparison of results of subjective sedation scoring, physical examination variables, and IOP and VPD measurements in 8 healthy equids at baseline (time 0; immediately prior to drug administration) and predetermined time points after oral administration of a single dose of trazodone (approx 6 mg/kg).

	Time (h)							
Variable	**0**	**0.5**	**1**	**2**	**4**	**8**	**12**	**24**
Sedation score*	0	1 (0–1)	1 (0–1)	1 (0–1)	1 (0–1)	1 (0–1)	0.5 (0–1)	0
Heart rate (beats/min)	38.0 ± 7.1	42.5 ± 10.2	39.5 ± 7.8	35.5 ± 8.7	33.5 ± 8.0	33.0 ± 6.7	33.0 ± 7.3	40 ± 8.8
Respiratory rate (breaths/min)	16.5 ± 5.4	18.3 ± 7.4	15.3 ± 5.2	16.3 ± 7.0	13.0 ± 4.1	12.5 ± 4.0	14.0 ± 2.1	17.5 ± 6.0
Rectal temperature (°C)	37.36 ± 0.39	36.91 ± 0.33	36.34 ± 0.48†	35.76 ± 0.55†	35.83 ± 0.44†	36.45 ± 0.70†	37.53 ± 0.76	37.56 ± 0.33
IOP (mm Hg)	25.1 ± 3.2	18.1 ± 2.7†	18.3 ± 2.1†	19.2 ± 2.1†	20.4 ± 3.2†	20.6 ± 3.3†	22.6 ± 2.6	23.1 ± 6.1
VPD (mm)	12.9 ± 2.8	11.7 ± 1.9†	12.3 ± 2.0	12.1 ± 2.0	12.1 ± 2.0	12.1 ± 2.0	12.1 ± 2.0	12.4 ± 2.0

Food was withheld from all equids from 12 hours before to 12 hours after drug administration. Data are reported as mean ± SD or median (range).

*Subjectively assessed on a scale from 0 (no sedation) to 3 (deep sedation) on the basis of unstimulated behavior and response to a noise created by a handclap performed outside the horse's line of vision. †Value is significantly ($P < 0.05$) different from that at baseline.

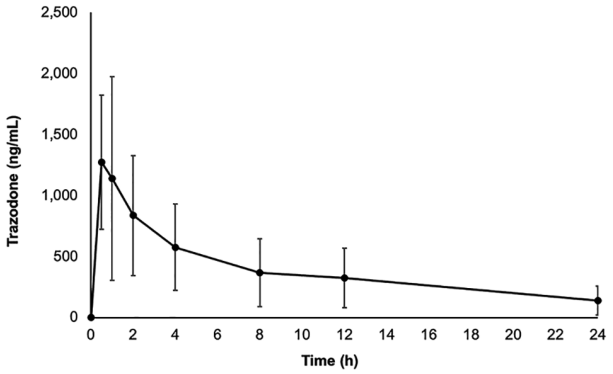

Figure 1—Mean ± SD plasma concentrations of trazodone at baseline (time 0; immediately prior to drug administration) and at predetermined time points after oral administration of a single dose (approx 6 mg/kg) to 8 healthy equids. Body weight of the animals was estimated by measurements as previously described.[9] A trazodone dose of 6 mg/kg was calculated and rounded to the nearest whole 50-mg tablet; tablets were ground and mixed with tap water and corn syrup for administration.

tility was not analyzed by statistical means because of the limited scoring range; however, most horses had normal gastrointestinal motility (score of 0 for 44/64 assessments) throughout the study.

Mean IOP was significantly decreased from the baseline measurement at all time points from 0.5 (mean difference, 7 mm Hg) to 8 (mean difference, 4.44 mm Hg) hours after administration of trazodone (Table 1). Mean VPD was significantly decreased from the baseline measurement 0.5 hours after drug administration (mean difference, 1.19 mm). Mean rectal temperature was significantly decreased from the baseline measurement from 1 (mean difference, 1.1°C) to 8 hours (mean difference, 0.95°C) after drug administration.

Plasma drug concentrations

Plasma concentrations of trazodone after oral administration were summarized **(Figure 1)**. Trazodone was detected in plasma of all equids, and plasma trazodone concentrations were > 130 ng/mL in all equids for ≥ 2 hours after administration. One equid (the same animal that had adverse behavioral signs) had a substantially different pharmacokinetic profile, compared with the rest of the study sample, with 2 peaks in concentration (420 and 383 ng/mL) noted during the 4 hours after trazodone administration; all other equids had a single initial plasma concentration peak followed by a slow tapering over the subsequent 24 hours. Pharmacokinetic parameters were tabulated **(Table 2)**.

Table 2—Pharmacokinetic parameters of trazodone after oral administration of a single dose (approx 6 mg/kg) to the 8 equids in Table 1.

Parameter	**Mean ± SD**
t_{max} (h)	0.75 ± 0.53
C_{max} (ng/mL)	1,439 ± 810
$AUC_{0-\infty}$ (ng•h/mL)	11,885 ± 8,040
AUC extrapolated (%)	16.8 ± 13.1
λ_z (h^{-1})	0.083 ± 0.036
$t_{1/2\lambda}$ (h)	9.96 ± 4.49

$AUC_{0-\infty}$ = Area under the plasma concentration-versus-time curve from time 0 to infinity. AUC extrapolated = Percentage of area under the concentration-versus-time curve extrapolated to infinity. λ_z = Terminal slope of the plasma concentration-versus-time curve. $t_{1/2\lambda}$ = Terminal half-life. t_{max} = Time to maximum concentration.

Discussion

In the present study, trazodone administered orally at a dose of approximately 6 mg/kg was associated with a significant decrease in mean IOP for 8 hours after the treatment was given and a transient significant decrease in VPD (identified 0.5 hours after treatment) in healthy equids. This drug dose produced signs of mild sedation for 8 hours after administration in 7 of 8 equids. One equid had delayed sedation, first observed 12 hours after drug administration, with excitable behavior and apparent hyperesthesia noted for the first 12 hours.

Trazodone acts at a variety of receptor types and has diverse pharmacodynamic effects in various species.[3,5,8] It acts in a dose-dependent manner on 5-HT (serotonin), H1 (histamine), and α_1-adrenergic receptors, as well as the serotonin reuptake transporter.[10]

Trazodone is thought to exert an effect on pupil size and IOP particularly through its interaction with α_1-adrenergic receptors, which are ubiquitous in the human eye.[11,12] Despite reports[7,13] in human medicine of increased IOP and induction of acute angle closure glaucoma following oral administration of trazodone, our results showed a significant decrease in IOP for up to 8 hours after trazodone administration to healthy equids. Although detailed adrenergic receptor mapping is not available for the eyes of equids, results of the present study suggested that distribution and subtype profiles for these receptors are sufficiently different from those in human eyes to cause an opposing and prolonged effect of trazodone on IOP. The prolonged lowering of IOP in our study sample could have been partly attributable to engagement of the unconventional outflow pathway or uveoscleral outflow, which is thought to have a more important role in aqueous humor dynamics in equids than in other species.[14–17] Additionally, the transient decrease in pupil size may have led to opening of the trabecular meshwork and facilitated outflow of aqueous humor via the conventional route, thus decreasing IOP in animals of the present study. Although the reduction in VPD corresponded to the onset of reduced IOP, the decrease in IOP was sustained for approximately 8 hours.

On the basis of findings in our study, it may be prudent to monitor the IOP of equids with preexisting ocular changes when trazodone is administered. Unless associated with uveitis, the lowering of IOP is not typically considered an adverse event. Equids in the present study had no evidence of uveitis (eg, aqueous flare, conjunctival hyperemia, or epiphora) to suggest the observed changes in IOP or VPD were caused by intraocular inflammation secondary to administration of this drug.

The time for trazodone absorption after oral administration in the present study (ie, mean ± SD time to C_{max} of 0.75 ± 0.53 hours) was consistent with that previously reported for horses by Davis et al[5] (0.37 ± 0.20 hours for a 7.5-mg/kg dose) but more rapid than that reported by Knych et al[4] (1.71 ± 0.42 hours for a 4-mg/kg dose). The apparent differences in absorption may have been attributable to differences in the drug formulations or doses or to the withholding of food for 12 hours prior to drug administration in the present study, allowing for greater absorption across mucosal surfaces. In previous studies, food was either not withheld[5] or was withheld for a shorter (8-hour) period.[4]

The plasma trazodone concentrations required for anxiolysis in nonhuman animals are not well described. In human literature, information on the concentrations required for anxiolysis is similarly lacking; however, concentrations of 130 ng/mL to 2 µg/mL are reported to have antidepressive effects.[18] All equids in the study reported here had plasma concentrations of the drug within the described range for antidepressive effects in people, with 7 of 8 equids showing clinical evidence of mild sedation consistently for 8 hours after drug administration and 4 of the 7 having these signs for 12 hours. Plasma concentrations of trazodone remained > 130 ng/mL in the study sample for ≥ 2 hours after administration, with only 1 equid having concentrations lower than this before the 12-hour time point. The 6-mg/kg dose administered in the present study resulted in a higher C_{max} (1,439 ng/mL), compared with the previously described 4-mg/kg oral dose in horses in another study[4] (1,392 ng/mL), and a lower C_{max} than described for 7.5- and 10-mg/kg oral doses (2,450 and 4,070 ng/mL, respectively).[5] Overall, the pharmacokinetic profile of mean plasma trazodone concentrations observed in our study was similar to those described previously. For sedative effects to be observed, it is assumed that higher circulating drug concentrations are required than for anxiolysis; the 6-mg/kg dose produced effective sedation in most horses in our study sample.

Adverse effects of trazodone in this study included moderate sweating in 4 equids and excitement and hyperesthesia in 1 equid. These signs were minor and self-limiting in all cases. The equid that developed adverse behavioral effects had these signs, with no evidence of sedation, from 0.5 to 8 hours after drug administration. Consistent mild sedation of this equid was noted at the 12-hour time point, resolving by 24 hours after drug administration. The pharmacokinetic profile of the drug for this equid was distinctly different from the others, with 2 plasma concentration peaks instead of 1, a lower C_{max} (420 ng/mL vs a mean of 1,439 ng/mL for the entire study sample), and persistently low drug concentrations throughout the study period. This equid had an excitable nature prior to initiation of the study. The IOP decreased from the baseline measurement in this equid, consistent with results for the other animals in the study, despite the lack of sedation. These findings suggested that responses to and some effects of trazodone can vary among individual equids when the drug is administered for sedation. It is possible that a lower dose, as previously described, would result in fewer adverse reactions; however, this could also reduce the sedative effects.

The present study had several limitations. The lack of a blinded investigator and control animals that had placebo treatment during the study interval created potential biases in subjective assessments after trazodone administration. In an effort to reduce bias, 2 investigators performed behavioral observations, and a consensus sedation score was used. For consistency, 1 investigator was designated for all IOP measurements, and 1 was designated for all VPD measurements. Administration of tablets was achieved by crushing the tablets and suspending them in a sweetened liquid for oral administration by syringe. Nasogastric intubation for drug administration may have allowed more precise delivery of the calculated dose, but this was considered likely to affect physiologic variables and the sedative effects of the drug by caus-

ing stress at the start of the study. The dose for each equid was calculated on the basis of body weight as assessed with a measuring tape method because a weight scale was not available. This method for weight measurement is inherently subject to error, although the likely degree of error was considered small according to the clinicians' experience.

The results of this and other studies suggest that trazodone may be useful as a sedative for equids that require stall rest, although individual variability and the potential for effects on ocular variables warrant consideration before clinical use. Further research is required to assess the safety and clinical effects of trazodone in equids, particularly when given to equids with ocular conditions or as a treatment course over time (eg, for a period of confinement). Additional research into appropriate withdrawal time is also necessary before administration of this medication to equine athletes.

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Footnotes

a. Hospira, Lake Forest, Ill.
b. Short Term/DayCath IV catheter, Mila International Inc, Florence, Ky.
c. Zydus Pharmaceuticals, Pennington, NJ.
d. TonoVet, Jorgensen Laboratories Inc, Loveland, Colo.
e. Cardinal Health, Dublin, Ohio.
f. TSQ Vantage, Thermo Scientific, San Jose, Calif.
g. Product, Thermo Scientific, San Jose, Calif.
h. 1100 series, Agilent Technologies Inc, Palo Alto, Calif.
i. Phoenix WinNonlin, version 8.1, Pharsight Corp, Princeton, NJ.
j. SAS, version 9.4, SAS Institute Inc, Cary, NC.

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