Effects of domperidone on digital laminar microvascular blood flow in clinically normal adult horses

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**Objective**—To determine effects of domperidone and acepromazine maleate on microvascular blood flow in digital laminae of clinically normal adult horses.

**Animals**—8 clinically normal adult horses (4 mares and 4 geldings).

**Procedures**—In a 4-period crossover study, domperidone was administered PO at 1.1 mg/kg and 5.5 mg/kg and IV at 0.2 mg/kg; acepromazine was administered IV at 0.04 mg/kg. The washout period between treatments was 1 week. A 3-minute measurement of laminar microvascular blood flow (LMBF) was obtained with laser Doppler flowmetry. Baseline measurements were obtained at –2, –1, and 0 hours prior to administration of drugs. Post-treatment measurements were obtained at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12 hours. Percentage change from baseline values in LMBF for each treatment was subsequently calculated.

**Results**—Oral administration of domperidone at 1.1 mg/kg and 5.5 mg/kg significantly increased LMBF, compared with baseline values, beginning 4 hours after administration, and this effect persisted for at least 8 hours. Intravenous administration of domperidone at 0.2 mg/kg significantly increased LMBF; compared with baseline values, at 10 and 12 hours after administration. Administration of acepromazine (0.04 mg/kg, IV) significantly increased LMBF, compared with baseline values, at 3, 5, 8, and 10 hours after administration. No adverse effects of drugs were detected in any horse.

**Conclusions and Clinical Relevance**—Domperidone may be useful for preventing vasoconstriction and reduction in LMBF believed to occur in horses with laminitis, but additional research of the drug’s effects in horses with laminitis is required. (Am J Vet Res 2010;71:281–287)

Laminitis is characterized by inflammation and destruction of the cellular bond between the dermal and epidermal laminae of the equine digit. Laminitis has a multifactorial etiology; proposed causes include digital hemodynamic disturbances, accumulation of matrix metalloproteinases, local digital cytokine gene expression, infiltration of the sensitive laminae with leukocytes, platelet activation, and release of monamines into the general circulation from the cecum and colon. Periods of laminar vasoconstriction can also occur during the developmental phase of laminitis induced with black walnut extract and by ingestion of excess dietary carbohydrates (carbohydrate overload). Counteracting this vasoconstriction may be beneficial in preventing laminitis or in treating horses for laminitis.

Domperidone has been suggested as a potential therapeutic agent for horses with laminitis. In the patent application for domperidone, 6 cases of laminitis in horses were reported as evidence of potential efficacy. Those horses, which were in various stages of laminitis, were treated with domperidone (1.1 mg/kg, PO, q 12 h or q 24 h); all had signs of clinical improvement in gait within 2 days after initiation of treatment.

In horses, the smooth muscle of digital blood vessels constricts in response to catecholamines (via \( \alpha_1 \)- and \( \alpha_2 \)-adrenoceptors) and serotonin (via 5-HT\(_{2A}\) and 5-HT\(_{1B}\) receptors). This smooth muscle appears to be 20 to 40 times as sensitive (in vivo) to the vasoconstrictor actions of 5-HT as are other peripheral blood vessels. Dopamine is an endogenous catecholamine with various cardiovascular effects. In dogs, it causes constriction of femoral blood vessels via postsynaptic \( \alpha_2 \)-adrenoceptors. In horses, it causes significantly greater constriction (in vitro) in digital arteries than in digital veins. Thromboxane \( \Lambda_2 \) and 5-HT\(_{1B}\) play a role in mediating lipopolysaccharide-induced digital hypoperfusion in horses.

**Abbreviations**

<table>
<thead>
<tr>
<th>5-HT</th>
<th>5-hydroxytryptamine</th>
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<tr>
<td>CPU</td>
<td>Capillary perfusion unit</td>
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<td>LMBF</td>
<td>Laminar microvascular blood flow</td>
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Domperidone, a benzimidazole, is a dopamine-2 receptor antagonist that may also act as an \( \alpha_1 \)-adrenoceptor antagonist and a 5-HT\(_3\) receptor antagonist. It does not readily cross the blood-brain barrier. The drug is used for the prevention and treatment of food and water intoxication in horses, increases follicular growth in seasonally anestrous mares, and has been used with altrrenoest and estradiol to induce lactation in barren mares. Domperidone also stimulates the return of healthy gastrointestinal motility in induced postsurgical ileus. Reports of the effect of domperidone on peripheral vasculature are conflicting. The drug reportedly increases blood flow to all segments of the eye, except the iris, in rabbits, but it also decreases blood flow in the forearms of humans when administered systemically.

Acepromazine maleate is a phenothiazine tranquilizer commonly used to treat horses with laminitis. In vitro, acepromazine is a potent arterial vasodilator in digits; in vivo, it causes dilation in the metatarsal artery and increased blood flow in the palmar digital artery. The drug inhibits \( \alpha \)-adrenoceptors resulting in peripheral vasodilation and subsequent systemic hypotension. It affects the cardiovascular system by depressing the central and sympathetic nervous system and by directly acting on smooth muscle (\( \alpha_1 \)-adrenoceptor antagonism) and cardiac muscle (transient sinoatrial arrest). The depression is achieved by blocking postsynaptic dopamine receptors centrally and \( \alpha \)-adrenoceptors peripherally.

Specific to its effects on limbs in horses, IV administration of acepromazine significantly prolongs palmar digital arterial blood flow in standing horses. The adrenergic blockade effect significantly increases arterial diameter, volumetric flow rate, and blood flow of the metatarsal artery. It also increases microcirculatory blood flow in coronary band and laminae by dilating the digital vasculature of healthy horses. Furthermore, IV administration of acepromazine at 0.066 mg/kg induces significant increases in blood flow through the digital arteries and laminae. The purpose of the study reported here was to determine the effect of domperidone administration on laminar microvascular blood flow in clinically normal adult horses and to compare this effect with the effect of acepromazine administration, which increases laminar microvascular blood flow.

Materials and Methods

Animals—Eight clinically normal adult mixed-breed horses (4 geldings and 4 mares) were selected randomly from the University of Tennessee’s teaching herd. The horses had no history of laminitis or lameness. Physical examination, hoof-tester application, in-hand gait evaluation, and lateral radiographs of all 4 feet were used to determine clinical normalcy. All horses had all 4 feet trimmed at the beginning of the acclimation phase of the study and were kept unshod for the duration of the study.

The horses were weighed when they arrived at the test facility and prior to each treatment. Horses were acclimated for at least 7 days in the environmentally controlled (ambient temperature range, 21\(^\circ\) to 23\(^\circ\)C) test facility. The feed, water, and housing conditions were the same for all horses during the period of acclimation and were the same as those used during the clinical phase of the study. Each was fed hay twice daily and had free access to water throughout the study. Horses were housed in 3.7 \( \times \) 3.7-m box stalls and bedded on straw. They were acclimated to stand quietly in equine stocks that were located approximately 23 m from their stalls. Each was physically examined daily. No vaccinations or medications, other than domperidone or acepromazine, were administered after the initiation of the acclimatization period. The study was approved by the University of Tennessee’s Animal Care and Use Committee.

Experimental design—A 4-period crossover design was used. In each period, horses received domperidone administered PO at 1.1 mg/kg or at 5.5 mg/kg (5 times the therapeutic dose), domperidone administered IV at 0.2 mg/kg, or acepromazine maleate administered IV at 0.04 mg/kg. Each horse received all 4 treatments with a 7-day washout period between treatments. This washout period was based on a half-life of domperidone in humans, which is 7.5 hours, and the half-life of acepromazine in horses, which is 2.5 hours. Food was not withheld prior to treatment. Two horses were tested each study day, with a different limb tested each time. On the day before initiation of treatment, horses were ranked by descending body weights within sex, and treatment order and treatment limb were assigned such that the combination differed for each horse.

Instrumentation—Laminar microvascular blood flow was measured as described by use of a laser Doppler flow meter coupled to a laser Doppler satellite. The units were equipped with a diode laser that had a wavelength of 780 nm. Two multireceiver probes were attached to each laser Doppler unit. Each probe had 11 receiving fibers separated from the sending fiber by 1.2 mm. If the total backscatter (reflected light) from the laminae was too great to obtain a reading, an attenuating fiber that reduced the amount of total backscattered light by 50% was placed between the probe and laser Doppler unit. Both laser Doppler units were connected to an analog-to-digital conversion box coupled to a computer. Proprietary software was used to store, retrieve, and analyze the data. Measured values constituted the flux of RBCs, defined as the number of RBCs multiplied by their velocity, and were reported in CPUs. Before each measurement period, each laser Doppler unit and probe was calibrated according to the manufacturer’s recommendations. Briefly, each probe was inserted into a zeroing disk to obtain absolute zero, then into a colloidal suspension containing a known quantity of latex particles, to obtain a positive standard value of 250 \( \pm \) 12.5 CPUs. If a probe could not be calibrated, it was replaced.

Electrocardiography was performed by means of an ECG monitor, with electrodes placed in standard configuration. Output of the ECG monitor was connected to the analog-to-digital conversion box, and data were collected and stored on the computer by use of the same...
proprietary software that was used to collect and store data obtained from the laser Doppler unit.

Experimental protocol—On the evening prior to each treatment, a jugular vein in each horse was catheterized; the catheter was flushed every 6 hours with 6 mL of heparinized, isotonic saline (0.9% NaCl) solution. After the catheter was inserted, with the horse standing in stocks, an electric drill and a 3-flute end mill bit was used to drill four 8-mm-diameter holes on the dorsum of the selected hoof to the junction between the epidermal and dermal laminae. A template was used to ensure that every horse had identical probe locations relative to the coronary band. The proximal 2 holes were 2.5 cm distal to the coronary band. One of these holes was 1.25 cm lateral to the dorsal midline of the hoof wall, and the other was 1.25 cm medial to the dorsal midline of the hoof wall. The distal 2 holes were 2.5 cm distal to the proximal holes. One was placed 1.25 cm lateral to the dorsal midline of the hoof wall, and the other was placed 1.25 cm medial to the dorsal midline of the hoof wall. The correct depth was verified by placing a laser Doppler probe into the hole. The depth was considered correct when blood flow was reduced to ≤ 4 CPUs when arterial blood flow was manually occluded at the level of the proximal sesamoid bones. All holes were drilled by 1 investigator (JRC). The holes were covered with adhesive tape, and each horse was returned to its stall.

On the morning of each treatment period, each horse was walked approximately 22.9 m to the stocks. A laser Doppler probe was secured into each hole with a probe holder, a double-sided adhesive ring, and adhesive tape. Laminar blood flow was then measured at each site, and the depth of the probe within the hole was adjusted until a consistent value of LMBF was obtained. A tourniquet was placed at the level of the fetlock joint and inflated to 300 mm Hg. A 3-minute measurement of LMBF was then obtained with the tourniquet in place and inflated. This value was used to designate a no-blood-flow state or biological zero. During a no-flow state, a laser Doppler probe will still yield a reading because of Brownian motion of the blood cells and vasoemotion. This measurement was then subtracted from all subsequent measurements to obtain true physiologic measurements of LMBF.

After the tourniquet was removed, the limb was allowed to equilibrate for 5 minutes before the first baseline measurement (–2 hours) was obtained. After the initial baseline measurement was obtained, the horse was returned to its stall. Adhesive tape was used to cover the openings on the probe holders to prevent debris from entering the holes in the hoof wall while a horse was in the stall. Additional baseline measurements were obtained at –1 hours and immediately prior to treatment (0 hours). Posttreatment measurements were obtained at 30 minutes and at 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12 hours. Electrocardiogram readings, rectal temperature, and pulse and respiratory rates were obtained at the same time LMBF measurements were obtained. All treatments were administered at the same time each day. All horses were monitored for clinical signs of lameness or laminitis (eg, shifting weight and changes in digital pulse quality, hoof temperature, and ability to lift the contralateral limb easily) in the tested limb at the same intervals. Changes in digital pulse quality and hoof temperature were assessed subjectively by means of digital palpation. Horses were also evaluated during the different test periods to ensure that lameness or laminitis had not developed in a previously used foot.

During the washout period, rectal temperature and pulse and respiratory rates as well as evidence of lameness or laminitis were evaluated daily. At the completion of the study, the probe holes were sealed with acrylic or silicone caulk.

Data collection—Signal averaging was used to obtain 3-minute measurements of LMBF at each of the 4 Doppler probe sites at each time point; data acquisition was triggered on the upslope of the R wave of the ECG. In a previous study, we had triggered data acquisition on the upslope of the arterial blood pressure wave, but it has been reported that triggering data acquisition on a portion of the ECG wave is acceptable and less invasive. The number of data points obtained varied with heart rate. The mean duration of the upslope of the R wave was 0.25 seconds, and because the data collection rate was preset at 64 measurements/s, 16 data points were collected during a 0.23-second period. For example, if the heart rate was 40 beats/min, then 1,920 data points were acquired for each 3-minute reading from each probe site. Data from all 4 probe sites were averaged to obtain a composite LMBF in the toe region for a given period.

Because signal averaging was used, a horse did not require continuous instrumentation, thus eliminating excessive movement attributable to inactivity and boredom, and could be disconnected from the equipment and returned to the stall between measurements.

Statistical analysis—Prior to data analysis, the measurements obtained for biological zero were subtracted from the baseline and posttreatment measurements. All adjusted measurements at each time point from all 4 sites on each hoof were averaged. These 4 means were then averaged within a period to provide 1 value at each time point. If fewer than 2 sites were recorded on a given hoof within a given measurement period, the result was considered a missing datum point. Baseline measurements (–2, –1, and 0 hours) were averaged together to yield 1 baseline measurement for each horse and treatment.

An ANOVA appropriate for repeated measures was used to evaluate the effects of treatment, time, and treatment-by-time interaction on the percentage change from baseline in LMBF. A compound symmetric structure was assumed for the covariance matrix. When the time by treatment interaction was significant (ie, P < 0.05), within-time treatment effects were evaluated at each time point. When treatment effects within time were significant, pairwise comparisons among the treatments were made. When the time-by-treatment interaction was not significant, the main effect of treatment on LMBF was evaluated. If the main effect of treatment was significant, treatment groups were compared, as described previously. Additionally, the percentage change in blood flow at each time point for each treatment was compared with 0 by use of a t test.

Rectal temperature and pulse and respiratory rates were analyzed via repeated-measures ANOVA, as de-
scribed previously, including the mean pretreatment measurements as a covariate. Because no horse became lame or developed clinical signs of laminitis, lameness or laminar inflammation was not statistically analyzed. A value of P < 0.05 was considered significant for all analyses.

Results

Physiologic variables and adverse effects of drugs—Age of the 8 randomly selected horses ranged from 4 to 15 years (median, 9.5 years) and body weight ranged 391 to 580 kg (median, 512 kg). No significant changes in rectal temperature and pulse rate were detected after domperidone or acepromazine was administered. Respiratory rates decreased significantly only after acepromazine was administered. These values remained within reference limits the day after each treatment period. No adverse effects were detected at any point. No horse developed signs of laminar inflammation or lameness during the study.

Effects of treatment on LMBF—Oral administration of domperidone at 1.1 mg/kg increased blood flow significantly from baseline at 4, 5, 6, 7, 8, 10, and 12 hours after administration (Table 1). Oral administration of domperidone at 5.5 mg/kg caused a significant increase in blood flow from baseline at 4, 6, 8, 10, and 12 hours. Intravenous administration of domperidone at 0.2 mg/kg increased blood flow significantly from baseline but only at 10 and 12 hours after administration. Intravenous administration of acepromazine at 0.04 mg/kg caused a significant increase in blood flow from baseline at 3, 5, 8, and 10 hours but not at 4, 6, 7, and 12 hours.

Discussion

In the study reported here, the effects of domperidone administration on LMBF were examined in healthy horses. The effects of both doses (1.1 and 5.5 mg/kg) of domperidone administered PO on LMBF were similar in time of onset of action and duration of activity to those of acepromazine administered IV, but domperidone administered IV at 0.2 mg/kg had less effect on LMBF than did the acepromazine. Acepromazine maleate, rather than a vehicle, was used as a positive control treatment because it had been used as a control treatment in a similar study.1

With regard to basic physiologic variables, the lack of change in rectal temperature and pulse rate and the lack of adverse effects after domperidone was administered are important if domperidone is to be administered to horses at risk of developing laminitis. The failure of lameness to develop in our study indicated that drilling a hole into the junction of the epidermal and dermal laminae induced minimal to no laminar inflammation. On the other hand, a decrease in respiratory rate after administration of acepromazine maleate has been reported.31

To our knowledge, the veterinary literature does not contain any pharmacokinetic data pertaining to PO administration of domperidone in horses. Therefore, insights into the pharmacokinetics of domperidone must be inferred from studies32,37,43 of absorption and clinical effect. One group of investigators administered domperidone (1.1 mg/kg) PO in 454 g of a corn-and-dry-molasses mixture to gravid mares and reported efficacy of treatment for fescue toxicosis.37 Another group reported an increase in the blood prolactin concentration within 4 hours after domperidone was administered PO to mares in a molasses-based carrier.39 These concentrations remained high for 24 hours after 1 dose. In that report,39 although domperidone was administered at the same time each day, no mention was made as to whether food was withheld from the mares between treatments.

Some effects of domperidone have been investigated in horses with pituitary pars intermedia dysfunction. In 1 study, investigators found that administration of domperidone (2.5 mg/kg, PO) to affected horses resulted in an endogenous plasma concentration of adrenocorticotropic hormone that was 2.9 times baseline values at 4 hours after administration. The investigators remarked that a disadvantage of using domperidone is that the drug is not available in a parenteral form. They were also concerned that administration PO added a degree of uncertainty to results of the domperidone response test because a horse might ingest less than the desired amount because of poor administration

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Domperidone (1.1 mg/kg, PO)</th>
<th>Domperidone (5.5 mg/kg, PO)</th>
<th>Domperidone (0.2 mg/kg, IV)</th>
<th>Acepromazine (0.04 mg/kg, IV)</th>
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</thead>
<tbody>
<tr>
<td>0.5</td>
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<td>114 (82–164)</td>
<td>119 (83–166)</td>
<td>115 (76–189)</td>
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<td>113 (72–146)</td>
<td>118 (87–164)</td>
<td>134 (63–248)</td>
</tr>
<tr>
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<td>133 (89–161)</td>
<td>114 (78–152)</td>
<td>114 (83–162)</td>
<td>128 (90–230)</td>
</tr>
<tr>
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<td>133 (100–201)</td>
<td>114 (87–136)</td>
<td>116 (87–165)</td>
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</tr>
<tr>
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<td>147* (66–303)</td>
<td>141* (91–228)</td>
<td>133 (84–199)</td>
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<tr>
<td>5</td>
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<td>124 (85–196)</td>
<td>119 (72–152)</td>
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<td>121 (72–203)</td>
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<td>136 (68–300)</td>
<td>131 (84–173)</td>
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<td>130 (111–194)</td>
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<td>185* (66–510)</td>
<td>138* (97–192)</td>
<td>134 (76–250)</td>
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*Value is significantly (P < 0.05) greater than baseline values (100%) measured on the 2 days preceding each treatment and immediately before the study began. Each set of baseline measurements was averaged together to yield 1 measurement for each horse and treatment.
technique. Also, a horse with delayed gastric emptying might not absorb enough of the drug to stimulate a response within 4 hours after administration, resulting in a false-negative test result. In another study, domperidone paste administered PO at a dose of 3.3 mg/kg to affected horses that had free access to water and hay 48 hours before testing caused an increase in adrenocorticotropic hormone plasma concentration within 4 hours after administration.

In the present study, the slow onset of action when domperidone was administered PO may have been because food was not withheld from horses prior to treatment or because of delayed gastric emptying or poor bioavailability of the drug. In humans and rats, plasma concentrations of domperidone peak later in fed subjects than in unfed subjects (30 minutes vs 120 minutes for humans and 15 minutes vs 30 minutes for rats) after PO administration.①② The drug may be absorbed directly from the stomach of rats from which food was withheld.③ Whether food should be withheld from horses when domperidone is administered PO is not specified on the drug insert of the commercially available domperidone product manufactured for horses.④ Other investigators have suggested that delayed gastric emptying could delay onset of action of domperidone.⑤

Poor bioavailability could also account for the delayed onset of action in the study reported here. In a study⑥ in which domperidone was administered PO to humans, bioavailability of the drug was low (13% to 17%). The investigators speculated that the low bioavailability was a result of incomplete absorption and a first-pass effect. They remarked that the bioavailability of orally administered domperidone is further decreased by increasing the pH of the stomach by administration of an antacid medication. Delayed onset of action and low plasma concentrations have also been reported with other drugs administered PO to horses.⑦⑧

The delayed response to domperidone, when administered IV, may be related to a concentration-dependent receptor system, whereby a high plasma concentration of domperidone is associated with little effect, but as plasma concentration decreases, an effect occurs. This could occur if domperidone acted at 2 types of receptors. At a low concentration, domperidone could have a higher affinity for a receptor responsible for vasoconstriction, resulting in a more pronounced vasodilatory effect, whereas at a higher concentration, domperidone could also bind (and block) a second vasodilatation-inducing receptor, causing vasoconstriction and thereby dampening the vasodilatory effect that occurred at a lower concentration. Such an effect has been reported for other drugs. For example, agents that block β-adrenoceptors at a low concentration antagonize the cardiostimulant effects of catecholamines but at a high concentration also cause cardiostimulation.⑨ These cardiostimulant drugs, known as nonconventional partial agonists, antagonize the effects of catecholamines through a high-affinity site but cause cardiotimulation mainly through a low-affinity site at myocardial β1-adrenoceptors.⑩ In dogs, dopamine administration results in a biphasic hemodynamic response in peripheral arteries, first causing vasoconstriction via α-adrenoceptors, then vasodilation via dopaminergic receptors.⑪ In humans, epinine reportedly has a dose-dependent separation of dopaminergic and adrenergic effects whereby low doses of dopamine and epinine exert effects only at dopamine receptors but do not activate α- or β-adrenoceptors.⑫ At higher doses, dopamine and epinine appear to have a different pattern of receptor activation: although dopamine exerts a mild β1-adrenoceptor stimulating effect because it lacks β2- and α-adrenoceptor activity, epinine appears to activate β1-, β2-, and α-adrenoceptors to approximately the same degree.⑬

It is possible that there are 2 interconvertible states of central dopamine-2 receptors containing high- and low-affinity binding sites;⑭ these 2 sites of the dopamine-2 receptors might also be present in the peripheral vasculature. Central dopamine-2 receptors also appear to have 2 functionally independent, distinct, G-protein coupling domains,⑮ as they are coupled to multiple transduction pathways, and these pathways may be activated by different receptor states. Whether a high-affinity or low-affinity state exists for domperidone is unknown.

Another explanation for the delayed response to IV administration of domperidone in the present study is that the vascular beds of laminae in horses could be more specialized than other peripheral vascular beds. In horses, control of the laminar vascular bed is a complex and poorly understood process. Acepromazine increases blood flow proximal to the digit, but at the same time, LMBF only mildly increases.⑯ That finding suggests that the equine laminar vascular bed is controlled by mechanisms different from those that control more proximal vasculature. Several studies⑰⑱⑲ have added greatly to our knowledge of regulation of LMBF. Results of those studies suggest that the regulatory mechanism of the laminar veins is different from that of the laminar arteries and that laminitis may be caused by a selective dysfunction of laminar veins. The studies also revealed that several receptor agonists and antagonists are involved in the regulation of LMBF.

The slow onset of action of domperidone after it was administered IV in the present study may have been because the dose was less than the optimal dose for investigation of the effects of domperidone on LMBF. Additional investigations are needed to determine the optimal dose for restoring LMBF.

In our study, IV administration of acepromazine resulted in a significant increase in LMBF from baseline at 3, 5, 8, and 10 hours but not at 4, 6, 7, and 12 hours. This finding conflicts with that of another study⑳ in which acepromazine (0.04 mg/kg, IV) had no significant effect on LMBF. The discrepancy in results may be attributable to the fact that in the present study, more horses were used (8 instead of 3), more probes were inserted in each foot (4 instead of 2), and measurements were obtained from all 4 feet rather than only the forefeet. A different group of investigators found that IV administration of acepromazine at 0.066 mg/kg causes a significant increase in digital blood flow within 15 minutes after administration that persists for 75 minutes.⑛ In their study, a mild but nonsignificant increase in laminar perfusion was also identified; this increase approached but did not attain significance at 45 and 60 minutes after treatment. Measurement of digital blood
flow ceased at 150 minutes after administration, and so it is unknown whether digital flow increased after this time. In our study, an increase in LMBF was detected within the first 30 minutes after administration of acepromazine, but this increase did not become significant until 3 hours after administration. Laminar perfusion remained increased for 7 hours. Another difference between the 2 studies is that we measured LMBF at 4 sites within each hoof, whereas the other investigators measured LMBF at only 1 site. Measurement of multiple sites within a given area increases the accuracy of the measurement technique and allows for a composite measurement for a given area. In addition, signal averaging was used in our study to allow for intermittent measurements for an extended period, whereas it was not used by the other investigators. Lastly, the laser Doppler probes used in the present study were specially made for measurement of LMBF. The probes have 11 receiving fibers, which increase their sensitivity and allow for receiving weaker signals from deeper in the tissue. Whereas the other investigators used a 3-mm needle probe, the fibers used in our study allowed for a depth of penetration in the 4- to 5-mm range versus the standard 2- to 3-mm depth.

Diurnal variation might explain changes in blood flow with time in the present study, but another study in which healthy horses were used revealed that LMBF does not change significantly during a 12-hour period after oral administration of deionized water. The hypothesis that LMBF does not change with time is supported by the findings of other studies as well. For example, no change in palmar digital arterial blood flow was detected during a 6-hour period following administration of isotonic saline solution to horses, and no change in laminar perfusion was detected after administration of isotonic saline solution during a 4-hour period. Hoof wall temperature has been used as an indirect measurement of laminar perfusion. The surface temperature of the hoof wall does not appear to change significantly during a 24-hour period in clinically normal horses. As long as ambient temperature is controlled, temperature of the hoof wall reportedly remains constant for a 30-hour period. Therefore, it appears that there is no significant diurnal variation on digital or laminar blood flow, as long as environmental temperatures are kept constant.

Inflammation of the laminae attributable to drilling of holes in the hoof wall could also increase LMBF with time. But the dermal laminae were never invaded by the drill bit in our study, and no blood was observed. Consequently, no signs of laminar inflammation or lameness were evident in any horse during or after the study.

References


c. Domperidone dissolved in DMSO, Dales Pharmaceuticals, a division of Dechra Pharmaceuticals, Skipton, North Yorkshire, England.

d. VEDCO Inc, St Joseph, Mo.

e. PeriFlux 4001 Master, PERIMED Inc, Smithtown, NY.

f. PeriFlux 4002 Satellite, PERIMED Inc, Smithtown, NY.

g. PF 412 multireceiver probe, PERIMED Inc, Smithtown, NY.

h. PF 423 attenuator fiber, PERIMED Inc, Smithtown, NY.

i. PF 472 A/D converter, PERIMED Inc, Smithtown, NY.


