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Ancillary Supplements for Horses with Laminitis and Metabolic Syndrome

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A number of useful ancillary supplements can aid the horse with laminitis, metabolic syndrome, Insulin Resistance (IR) and Pituitary Pars Intermedia Dysfunction (PPID). Before adding adjuncts, however, it is very important to have all the elements of correct treatment of these conditions.

THE FOUNDATION

Diagnosis, Diet Trim and Exercise (DDT+E) is the protocol for dealing with IR, PPID, and laminitis developed over many years by the ECIR group.¹ This approach continues to be developed as new information becomes available.

Diagnosis (first D) of IR or PPID is by laboratory confirmation from appropriately drawn and handled blood work. While laboratory tests are not always 100% accurate, they are the most accurate we have, and they are objective. Laboratory values can also be used to monitor progress. Without a firm diagnosis, it is impossible to know what treatment to use, and whether or not any particular diet, drug or supplement is working.

Diet and Drugs (second D) are the treatment arm of this protocol. Without the diet in place, no drug is going to work for IR. In PPID, the gold standard for treatment is pergolide. There is no substitute for pergolide, and without it, dietary methods alone are not going to work.

Trim (T) is often the hardest element to put in place. The concept is simple, but the practical application can be difficult for many people. The basic concept is for the external hoof wall to fit the internal structures of the foot like a glove.^{2,3} With laminitic horses, radiographs are often needed to determine where the internal structures are, because the external hoof is distorted.

Exercise (E) is the fourth part of this equation, and is very beneficial in controlling insulin, if the horse is able.⁴

DIAGNOSIS

The adrenocorticotrophic hormone (ACTH) test is most useful for the diagnosis of PPID. The thyrotropin releasing hormone (TRH) stimulation test, has a higher degree of sensitivity, but also a higher degree of false positives, perhaps leading to unnecessary use of pergolide. During the autumn seasonal rise, ACTH is still a very useful test if one adjusts the upper limit of the normal level to take the seasonal effect into account.

For diagnosing insulin resistance, the ECIR group uses the insulin and glucose proxies⁵, the G:I ratio and leptin, on blood values drawn from a non-fasting horse. Leptin can be tested at Cornell University.

Leptin, the satiety hormone, is a useful aid in distinguishing between IR at baseline, or IR due to PPID/ Cushing's. A horse that is IR at baseline will have a higher leptin than a horse that has high insulin levels due to Cushing's. IR horses are also often leptin resistant, which explains the ravenous appetite they can display.

DIET

Diet is the mainstay of treatment for insulin-resistant horses. These horses should be fed a grass hay with ESC (Ethanol Soluble Carbohydrates) plus starch of less than 10%. As a starting point, feed at a rate of either 1.5% of current weight, or 2% of ideal weight, whichever is the greater amount. The hay should have a digestible energy level of about 0.8 to 0.85 Mcal per pound. If the energy level of the hay is higher than that, it may be necessary to reduce the amount.

The next step is to provide minerals that are balanced to the hay, with a low-ESC/starch feed to carry the supplements. Add iodized salt, Vitamin E in a fat source, and ground flax seed separately.

Mineral ratios used to balance the diet are very important. Major mineral ratios, calcium to phosphorus to magnesium, should be 2:1:1. Ratios may be as low as 1.2:1 calcium to phosphorus, and calcium to magnesium, without any adverse bone effects.

The trace mineral ratio for iron to copper to zinc to manganese should be 4:1:3:3. Virtually all hays are high in iron and low in copper and zinc, requiring a significant amount of copper and/or zinc. Although there are some areas that are manganese deficient, manganese is less frequently needed. Most hays have more than enough chromium, making additional chromium unnecessary.

It is very important to avoid added iron. Many of these horses are already iron-overloaded. There has never been a case of diet-related iron deficiency in a horse over the age of one year.

SUMMARY

Supplements are unlikely to help if the diet is not appropriate. All aspects of DDT+E should be addressed before considering using any adjuncts. Too much focus on looking for supplements can take away time and energy from the real treatment for IR: diet, trim and exercise; or from PPID treatment: pergolide, diet, trim and exercise.

WHAT ANCILLARY SUPPLEMENTS ARE USEFUL ADJUNCTS?

Many herbal and supplement formulas and single ingredients used for diabetic humans work by lowering blood glucose. A 2012 study (deLaat, et al.)⁶ looking for Advanced Glycation End-products (proteins in tissue with a glucose molecule incorporated into them) found none of these products in the lamellar tissues of horses with laminitis, indicating that hyperglycemia was not involved in endocrine laminitis. Lowering glucose does not help IR horses, as most have normal blood glucose.

Cinnamon was considered an adjunct for IR in humans, because it can lower blood glucose and improve insulin sensitivity. A field trial of the ECIR Group horses using cinnamon was unrewarding. In some cases the glucose was lowered but the insulin was unchanged.

Chromium is very likely an essential mineral for mammals. Chromium is a non-essential element for plants, and is taken up passively if it is in the soil. Chromium was dubbed "Glucose Tolerance Factor" when incidental findings in human patients who were receiving complete intravenous feeding with solutions that did not contain chromium, developed marked glucose intolerance. When chromium is given to normal humans, it has no effect on glucose metabolism. When given to insulin-resistant or diabetic humans, there are some measurable results, although there is also conflicting evidence in the literature. One large study in humans showed an inverse correlation between metabolic syndrome and toe-nail chromium levels. Serum triglyceride levels were positively correlated with chromium; but insulin levels showed no clear relationship. Horses have changes in triglyceride levels with metabolic syndrome, but not to the same extent as humans.

There have been a number of animal studies involving chromium in veal calves, yearling horses, working horses, and dairy cows. These four groups of animals typically have diets high in grains. Some equivocal degree of improvement of glucose tolerance was shown with chromium supplementation. Possibilities affecting

results include the grain diet having lower chromium levels than a forage diet; the high-carbohydrate diet utilizing extra chromium as happens in humans; a higher level of chromium is needed when a high-carb diet is fed. These effects have not yet been separated out. Clinically insulin-resistant horses on an appropriate forage-based diet have not shown any positive effects from chromium supplementation.

Jiaogulan (*Gynostemma pentaphyllum*) is a Chinese herb harvested from a vine that is indigenous to southern China and some other parts of south-east Asia. A very non-toxic herb, it is used both as a natural medicine, and as a food source. For laminitic horses, one effect of jiaogulan is the counter-acting of elevated levels of endothelin-1⁷. Endothelin-1 is a protein in the body that is an extremely potent vaso-constrictor. Nitric oxide causes the muscles controlling the diameter of the blood vessels to relax; it also helps reduce platelet aggregation inside vessels. (Figure 1) The other side of the diagram in Figure 1 shows the opposite effect of endothelin-1 — vasoconstriction. Jiaogulan increases the production of nitric oxide by the cells that are lining the blood vessels⁸.

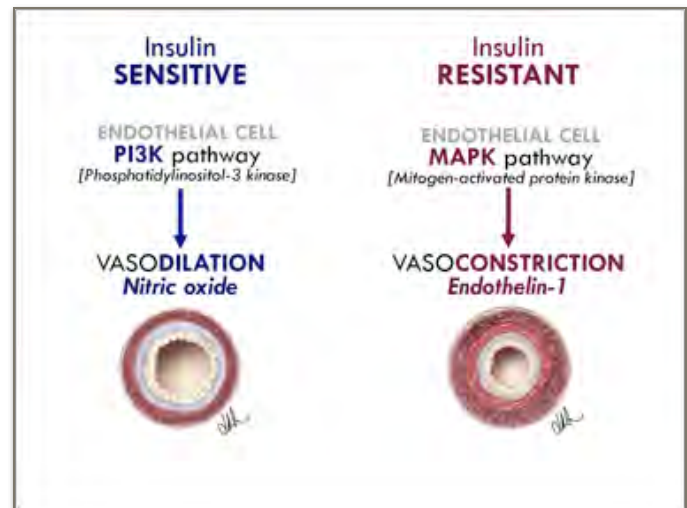


Figure 1

Nitric oxide synthase (NOS) is the enzyme that produces the nitric oxide. There are three forms that we know of: E-NOS, I-NOS, and N-NOS. E-NOS (endothelial nitric oxide) is the enzyme inside the lining of the blood vessels and is constantly being produced there at variable levels. This causes the blood vessel to relax and dilate, which inhibits clotting and causes the release of growth factor. If there is injury nearby, healing is encouraged.

I-NOS (inducible nitric oxide) is not normally active. There has to be an event to induce its activity, such as an injury or inflammation. I-NOS will itself cause inflammation, vaso-constriction, and clotting. It also causes thickening of the lining of the vessel, the first stage of arterio-sclerosis in humans.

N-NOS (neurologic nitric oxide) is produced inside the nervous system and is involved with pain transmission.

Jiaogulan increases the activity of e-NOS, and directly inhibits i-NOS.

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The Jiaogulan trial⁹ used 176 horses with laminitis, followed for periods of 3 months up to 2 ½ years. IR was confirmed, and they were screened for PPID. The requirements for DDT+E were met before the jiaogulan was started. Of these 176 horses, 75% of them were painful enough to be considered to require phenylbutazone treatment.

Dosage of the ground-leaf jiaogulan powder, *Gynostemma*, ranged from 1,000 to 2,000 mg per 500 lbs body weight, twice daily. In all subjects phenylbutazone was discontinued. The responses included more mental alertness, increased spontaneous movement, and improved circulatory effect as evidenced by an increased pinkness of the mucus membranes of the mouth. The dose was adjusted upwards until the increased pinkness was seen. There were no complications from the herb itself, but collections of serum, blood, and pus in the feet surfaced within the first two weeks in some horses. Phenylbutazone can inhibit the maturation of these collections, which results in ongoing pain. Trial results were as follows:

— 109 (61.9%) returned to pasture soundness at a walk with two days to two weeks of starting the *Gynostemma*. Surfacing of abscess collections is very common during the initial two to three weeks of treatment.

— 20 (11.4%) were nonresponders. No response was associated with poor control of the underlying medical problems or severe demineralization of the coffin bone.

— The remaining 47 animals (26.7%) showed improvement of 1 to 2 lameness grades. Amount of rotation of the coffin bone and degree of lameness at the start were not predictive of response.

Jiaogulan can be combined with other compounds that support the production of nitric oxide. Nitric oxide is produced from the amino acid L-arginine. L-citrulline is an end-product of that reaction, but it can also cycle back to L-arginine and thus be another source of nitric oxide. There are also various B vitamins that support this reaction. When L-arginine and jiaogulan are combined in a supplement such as Laminox (Uckele Health and Nutrition), production of nitric oxide is heightened compared to using either one alone.

For pain control and as a substitute for phenylbutazone, *Phyto-Quench* (Uckele Health and Nutrition) has been used by members of the ECIR Group for many years and has proven helpful to laminitic horses. *Phyto-Quench* is free of the potential negative side effects of NSAIDs: gastritis; colitis; reduced peripheral circulation; kidney damage; and delayed healing of many tissues documented with phenylbutazone use.

There is some effect from the anti-oxidant, but other factors are also involved in the pain relief. *Quercetin*, for example, included in a high dose in the *Phyto-Quench*, is present in a variety of foods and also grasses. Quercetin reduces the release of pain-sensitizing cytokines such as TNF-alpha¹⁰. It also has a direct effect, that can be blocked by naloxone (an opioid antagonist), suggesting that it is bonding to opioid receptors¹¹. The pain-relieving effects of morphine are increased when morphine is given with quercetin.

Other key ingredients in *Phyto-Quench* have been found to address pain. *Curcumin* is able to reverse the pain hypersensitivity found in diabetics by a direct normalizing effect on the nerve cells¹². *Ginger* has a similar effect. *Ginkgo* neutralizes the oxygen-free radicals produced during excessive nitric oxide production from the i-NOS enzyme, thus blocking that pain pathway.

Biotin is known to be involved in the response of the insulin receptor and the glucose transporter. It is also useful for hoof growth. The optimum dose of biotin is 20 mg daily.

Adaptogens are very useful adjuncts in helping laminitic horses. Adaptogens enhance the reactions to stressors when the reactions are too weak and modulate the reactions downwards when they are too strong. An adaptogen can both increase a stress reaction and lower it through the chain of the release of stimulating hormones that bind to adrenal receptors. In situations of high levels of binding hormones, the adaptogen will bind to receptors instead, reducing the effect of the hormone. In situations where there are insufficient hormones binding to receptors, the adaptogen binding to the receptor will produce an effect, less than that of the normal hormone, but more than no hormone at all.

Advanced Protection Formula, (APF) is a blend of well-known Chinese adaptogens, extracts of *Eleutherococcus senticosus*, *Schizandra chinensis*, *Rhodiola rosea* and *Echinopanax elatus*. ECIR Group members have found APF useful in relieving the lethargy and fatigue that is often present in PPID horses. It protects completely against the initial side effects of pergolide – reduced appetite and depressed attitude. APF is also very helpful with winter laminitis.¹³

Vitex agnus castus, or chaste tree, is a large shrub with a long history of use for hormonal modulation. It has been documented to influence prolactin, likely the hormone involved in the abnormal coat in Cushing's horses.

In 1999, an 11-month field trial¹⁴, started in late winter, was conducted with PPID horses and a standardized liquid extract of *Vitex*. All horses showed improvement in coat shedding, increased energy, more activity and possibly improvement in laminitis pain. Although it was difficult to differentiate between increased energy, and decreased pain, *Vitex agnus castus* also has a morphine-like effect in the brain, making decreased pain likely¹⁵. By fall it was obvious that there was improvement in the early PPID horses. Advanced PPID horses at that time were beginning to get a return of clinical signs with the seasonal rise. The trial was stopped at that point, and any horse that looked like advanced PPID was started on pergolide. The conclusion was that *Vitex agnus castus* was not a substitute for pergolide, but could provide symptomatic relief in mild cases of PPID.

A 2002 New Bolton study¹⁶ conducted a trial using chaste tree instead of pergolide, and found that it did not control ACTH levels. Most of the horses in the trial were advanced cases of Cushing's, and no effects on clinical signs were seen.

Between 2001 and 2004, the Laminitis Trust conducted a study¹⁷ that followed the horses for at least a year. Again, symptomatic relief occurred, but there was no reliable control of ACTH. This means that the pituitary adenoma growth and ACTH production are continuing unchecked. If pergolide is not started until the chaste tree is no longer controlling the clinical signs, higher doses of pergolide are needed and it is more difficult to normalize the ACTH. It is therefore not appropriate to use chaste tree as a substitute for pergolide even in early cases of PPID. It is a useful addition to pergolide to aid in shedding out. Caution is still advisable when using both pergolide and chaste tree, as there are no formal studies on the combined use.

SUMMARY

Ancillary supplements can be helpful for the IR and PPID horse. Treatment of these conditions requires a foundation of correct Diagnosis, Diet, Trim and Exercise (DDT+E). Adding ancillary supplements without paying attention to the appropriate protocol is worse than useless, and may be harmful

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