

# Effects Of SGLT2i On Triamcinolone-Induced Equine ID

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**This proposal will evaluate the degree to which joint injections with triamcinolone worsen insulin dysregulation in horses with ID and if use of canagliflozin at time of injection mitigates it.**



Laminitis (or founder) is a devastating disease of the equine foot that causes intractable suffering for affected horses and economic loss to the equine industry. Laminitis associated with endocrine disease is the most common form and has been associated with three common conditions: equine metabolic syndrome, equine Cushing's syndrome, and administration of steroid medications (with joint injections, for example).

The biology of these three separate conditions differs significantly in certain respects, but insulin dysregulation (ID) is known to be a single consistent characteristic shared by all three. Very little is known about laminitis that occurs after steroid administration, given that it is uncommon and there is no reliable experimental model to induce it; however, a very large number of horses receive steroids in joint injections, as this is an extremely common therapy used to treat equine osteoarthritis.

Triamcinolone acetonide (TCA) is a steroid that is frequently used for this purpose. Based on the large number of horses receiving joint injections to maintain athletic soundness as they age, cases of laminitis that occur as a complication of this treatment are inevitable. Further clarification of risk factors associated with laminitis in this setting would be helpful to design strategies to make this very useful therapy safer, given that the number of older horses (including those with Cushing's syndrome and EMS) engaged in athletic pursuits is increasing. The absorption and excretion of TCA following administration by various routes in horses (including in the joint) have been described. However, little is known about TCA's effects on insulin and glucose metabolism following administration in the joint (even though this is the most frequent route by which it is given, and this effect is highly likely to relate to its perceived risk of inducing laminitis). Since a consistent experimental model of steroid-induced laminitis has not yet been described, the mechanism by which these drugs create risk of laminitis remains unclear; however, systemic (IV, IM, or oral) steroid administration is known to induce ID.

Recently, new drugs for managing equine ID have been described, including sodium glucose cotransporter-2 inhibitors (SGLT2i; ex., canagliflozin, ertugliflozin, and velagliflozin); while these drugs are potentially very effective, they are expensive and may be associated with adverse effects with long-term use. However, short term use to prevent ID associated with joint injections may be an effective, novel use of these drugs in equine patients.

We propose to investigate the effects of TCA injected in the joint on systemic ID in horses with naturally occurring ID and the ability of canagliflozin (an SGLT2 inhibitor now used frequently to treat EMS patients) to prevent or decrease ID when given at the time of joint injection. Twenty-one adult horses GT 5 years of age will be screened for ID with an oral sugar test, enrolled if ID, and assigned to one of three groups (G1-3, n=7 per group). All horses will receive a joint injection of 20 mg TCA on Day 0, and assessments of systemic ID, including oral sugar test (baseline, Days 1, 3, 7, 10, 14, 30), IV insulin tolerance test (baseline, Days 1, 3, 7, 10, 14, 30), measurements of serum hormone concentrations (insulin, glucose, triglycerides, cortisol; baseline and Days 1, 3, 7, 14, 30), and serum biochemistry (baseline, Days 7, 14, 30) will be performed to determine effects of TCA given in the joint on clinically relevant measures of ID in horses with naturally occurring ID. Horses in G1 will receive TCA only; horses in G2 and G3 will receive canagliflozin (0.3 mg/kg by mouth once daily) starting the day of joint injection (one dose only for G2, 7 days for G3).

The information generated by this work will provide important information about this commonly used drug (TCA), as well as lay a foundation for future investigations of therapies that might be used to minimize ID associated with TCA joint injections and, therefore, the risk of inducing laminitis after this treatment. Further, if the results of this study provide evidence that administration of an SGLT2i around the time of joint injections reduces ID associated with steroid administration, they may then inform further

investigation of this strategy to create rational guidelines for risk management when using TCA in this manner.

**Importance to the Equine Industry:** Laminitis (or founder) is a devastating disease of the equine foot, and endocrine disease is currently the most common cause of laminitis in industrialized nations. This is a critically important economic and welfare concern for the equine industry worldwide. While equine metabolic syndrome-associated laminitis makes up the majority of cases encountered by equine veterinarians, laminitis associated with therapeutic steroid administration (such as joint injections) remains an important concern of veterinarians and horse owners alike, particularly since this treatment complication has proven difficult to predict and can be catastrophic for affected horses. Administration of steroids in joint injections is an extremely common therapy applied to treat orthopedic conditions, such as arthritis, that occur regularly in equine athletes. Drugs such as triamcinolone acetonide are frequently used for this purpose, and while the induction or exacerbation of laminitis following this type of treatment is thought to be rare, a recent study of laminitis associated with endocrine disease reported that horses that had received treatment with steroid medications in the past 30 days were 5.6 times as likely to develop laminitis than horses that had not received this treatment; this risk is very likely higher in EMS patients. Given the increasing prevalence of obesity, EMS, and equine Cushing's syndrome in populations of equine athletes, including horses in active competition, the likelihood that joint injections using triamcinolone might be performed on patients with underlying insulin dysregulation is high, and there is currently little clear information about how this therapy may affect control of the underlying endocrine disease, let alone the risk of laminitis. The risk of inducing insulin dysregulation with triamcinolone via joint injections is therefore of interest to equine veterinarians and horse owners, as well as ways to minimize this risk (such as use of SGLT2i's).