# Pharmacokinetic and clinical study of intra-articular insulin in healthy horses

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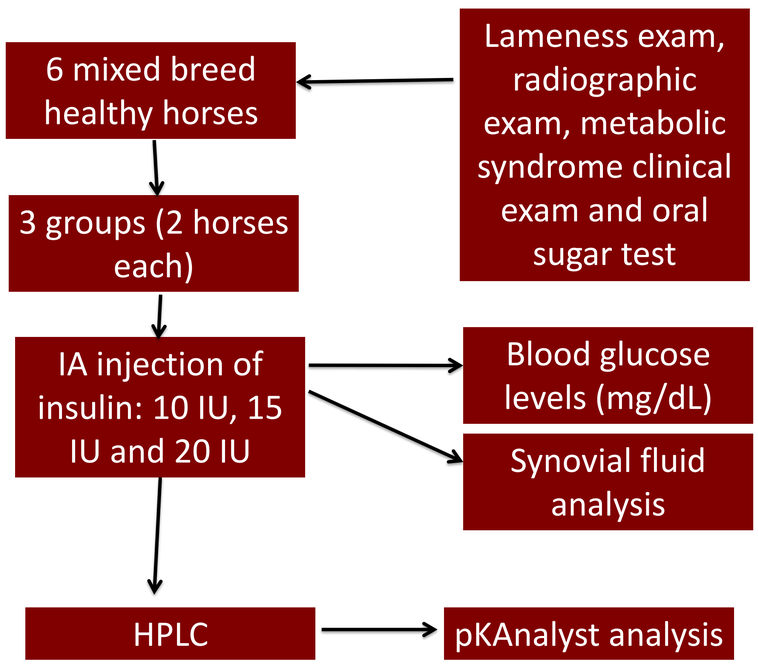
## Background

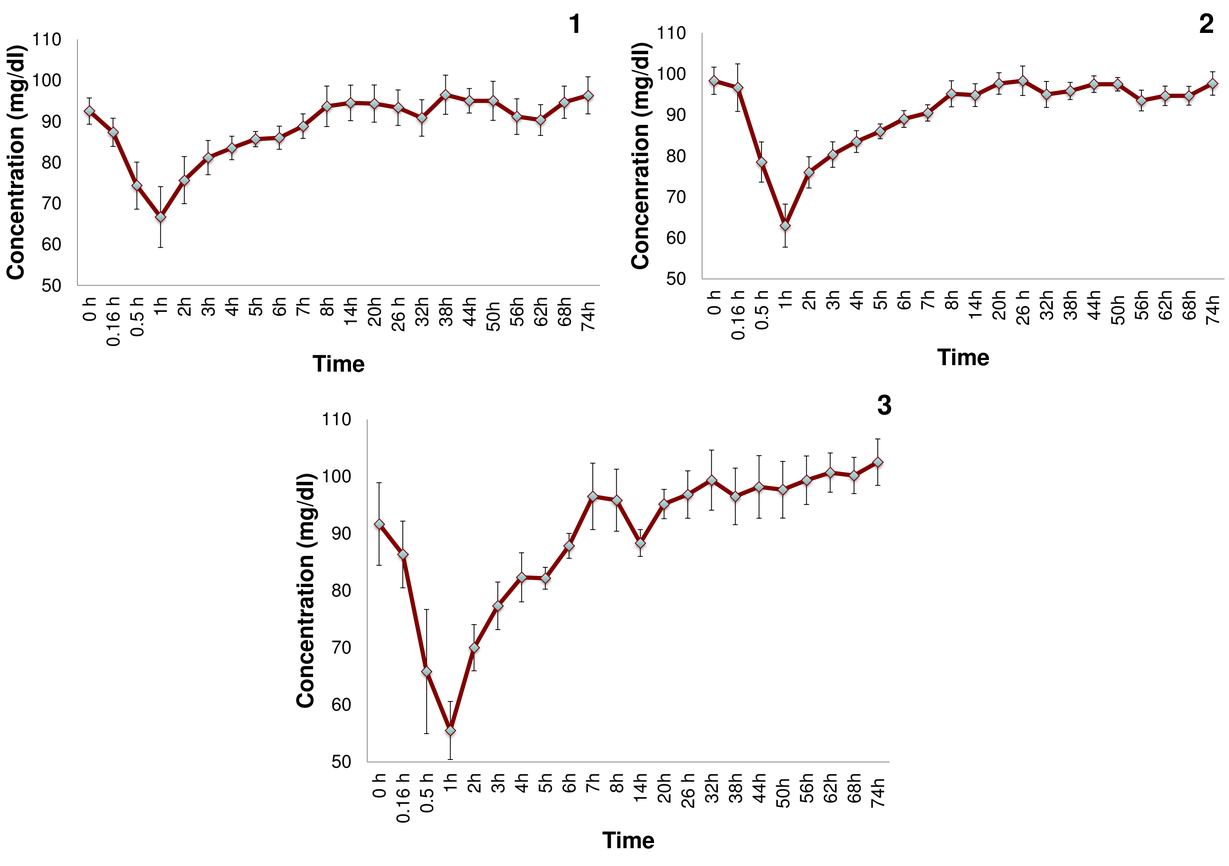
The horse has approximately 6,000 years of being domesticated, also it has been used by man kind for several athletic activities, from which we have various equine sports today. However, this activities make the horse an athlete, which makes it more prone to excessive loads to the bones, joints and soft tissues with their subsequent injuries, and because of that, equine sports medicine has been developing several combinations of treatments for those conditions in order to maintain their health for sports. Insulin has been used empirically for intra-articular (IA) injection without really knowing both its local (joint) and systemic effects and therefore, its dose. There´s scientific evidence that insulin produces mitosis in equine chondrocites *in vitro* with concentrations lower than 50 ng/ml, also it enhances type II collagen production.
The objective of this study was to determine the pharmacokinetic parameters of insulin injected directly into the horse´s joint; in order to know its therapeutic dose and also, if the insulin did not represent any adverse reaction both local (joint) in a cellular level, and systemic (blood glucose).

## Methods




## Results

Significant changes through time in blood glucose levels for the 3 doses (P<0.0001); no significant difference was found between synovial fluid protein and cell count in both treated and control (saline 0.9%) joints (P>0.05); also, no significant difference was found regarding synovial glucose levels between treated and control joints (P>0.05). HPLC revealed that the pharmacokinetic parameters are dose dependant, however, there was no significant difference when compared with the three different doses (P=0.9851).




**Figures 1-3 Blood glucose.** 1) 10 IU dose; 2) 15 IU dose; 3) 20 IU dose. All three doses showed a significant drop of glucose levels, that was restored within the 6-8 hours por IA injection of insulin. The 20 IU seemed to have more variation of parameters when compared with the 10 and 15 IU graph.

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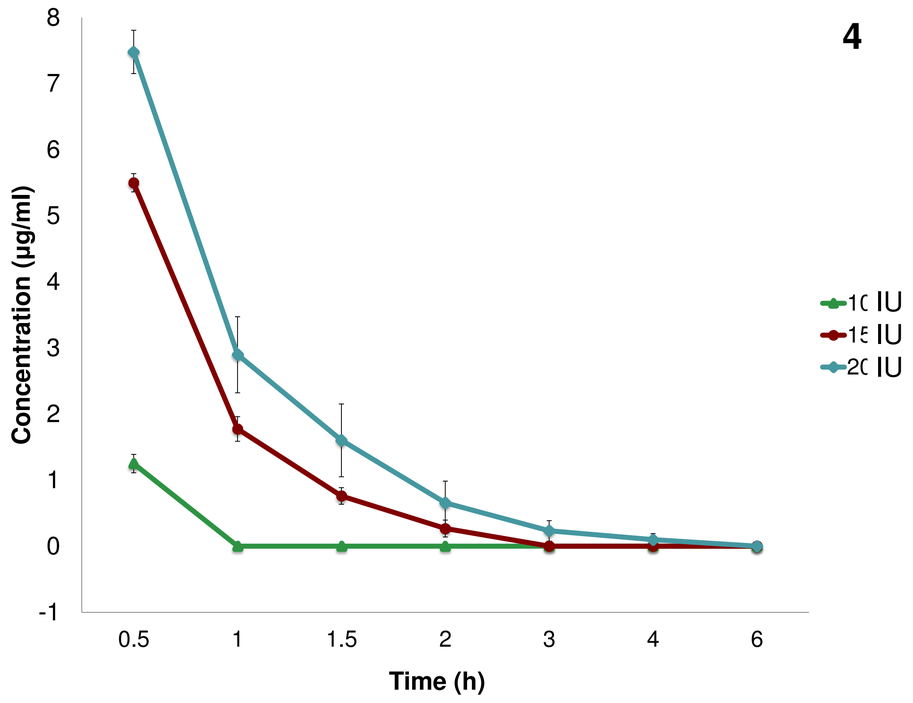


**Figure 4.** Withdrawal curve for the 3 different dosis (10, 15 and 20 IU). Every dose has its own AUC, which is dose dependant.

**Table 1. Pharmacokinetic parameters for the 15 IU dose of IA insulin.**

| Parameter | Result | Time (min) |
|---|---|---|
| Half life ($K_{AE}$ *Half*) | 0.199927931 | 11.99 |
| Time of maximum concentration ($T_{Conc}$ *Max*) | 0.288435035 | 17.30 |
| Area under the curve (*AUC*) | 5.15211030 | NA* |
| Residence Time (*Residence_Time*) | 0.576870070 | 34.61 |

**NA: Not applicable*

**Table 2. Pharmacokinetic parameters for the 20 IU dose of IA insulin.**

| Parameter | Result | Time (min) |
|---|---|---|
| Half life ($K_{AE}$ *Half*) | 0.232681513 | 13.8 |
| Time of maximum concentration ($T_{Conc}$ *Max*) | 0.335688466 | 19.8 |
| Area under the curve (*AUC*) | 7.37122310 | NA* |
| Residence Time (*Residence_Time*) | 0.671376931 | 40.2 |

**NA: Not applicable*

## Discussion and conclusions

Non of the 6 horses was lame or presented any clinical sign corresponding to equine metabolic syndrome (EMS) or insulin resistance (IR). Additionally, no evidence of osteoarthritis was found in the radiographic studies.

The changes seen in the synovial fluid analysis were due to needle trauma. No significant increase in protein and nucleated cell count was found. The most predominant cell type was mostly erythrocytes. These results suggest that the insulin used in this study represent no chance for an adverse local reaction to this drug.

Insulin injected into the horses joint has a first order kinetics. All pharmacokinetic parameters are dose dependant. However, insulin has a very short time within the joint, and it is insufficient if the goal of using it IA, is to repair articular cartilage. However, more studies are necessary regarding the duration of insulin in a cellular level in the joint. Since the 10 IU only gave one result at 30 min post injection, there was not possible to determine the pharmacokinetic parameters for that dose.

The recommended dose in this study for a 350-400 kg horse is no more than 20 IU/horse. Since the blood glucose had a significant drop seen at one hour post injection, we suggest that the horse must remain in observation for at least one hour post IA injection of insulin. In this study we used a small amount of horses (n=6), therefore more studies are needed in order to really determine a therapeutic dose of this drug when used IA.

Insulin shares the same receptor as IGF-1, so its intracellular effect for mitosis is by the same pathway (MAP-K), it also produces type II collagen, all of this in less proportion than IGF-1 itself.

This is the first *in vivo* study for the intra articular use of insulin, so it can be used as a base for subsequent studies regarding this drug.

## References

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