KETODOXAPRAM AS A TREATMENT FOR ATRIAL FIBRILLATION

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This study is to determine if Ketodoxapram is a promising novel treatment method for horses with atrial fibrillation.

Cardiac arrhythmias are frequently diagnosed in horses and can have serious consequences such as collapse or sudden death. Atrial fibrillation is the most common clinically important cardiac arrhythmia in equine athletes. Atrial fibrillation is found in about 0.3% of horses in the general equine population, and in up to 5% of racehorses. Although the mechanisms and consequences of atrial fibrillation are increasingly better understood, drug treatment options remain limited. Even in human medicine, the currently available medication is often ineffective and, in addition, there is a high risk of side effects and relapse after treatment. At the Faculty of Veterinary Medicine in Ghent (Belgium), horses are routinely treated with an intracardiac electrical shock under general anesthesia, with a success rate of about 95%. The electrical shock results in cardioversion of atrial fibrillation to normal sinus rhythm.

This treatment can world-wide only be carried out in a few highly specialized centers. To avoid this technical procedure, pharmacological treatment can be performed using drugs. Traditionally, horses with atrial fibrillation are treated with the drug quinidine sulphate, but this medication is increasingly difficult to obtain in many countries: the product is disappearing from the market because of the frequent side effects in humans and animals. Common side effects that occur after the administration of quinidine sulphate in horses include nasal swelling, depression, high heart rates, colic, diarrhea, weakness, laminitis, collapse and even sudden death. The success rate of quinidine sulphate treatment is about 60-80%, which is also considerably lower compared to the electrical cardioversion treatment. Other available drugs are even less effective, with a maximal success rate of about 50%, and also cause different side effects.

Studies in human medicine are currently evaluating drugs which target specific ion channels in the heart, the TASK-1 potassium channels. Drugs which inhibit these TASK-1 channels, such as ketodoxapram, could be a novel treatment option for atrial fibrillation. The TASK-1 channels are mainly expressed at the level of the atria, which minimizes the occurrence of side effects when a TASK-1 inhibitor such as ketodoxapram is administered. Specific blocking of the TASK-1 channels slows down the atrial fibrillation rate and allows cardioversion to normal sinus rhythm. Preliminary results of ongoing research by our group demonstrated that the TASK-1 potassium channel is also present in horses. Moreover, the equine and human TASK-1 channel are very similar. Therefore, intravenous treatment by ketodoxapram seems like an ideal candidate for pharmacological treatment of atrial fibrillation, especially short duration atrial fibrillation after exercise or anesthesia.

We will test ketodoxapram treatment in horses in which atrial fibrillation is induced by a pacemaker. This way we can evaluate the effect of ketodoxapram for treatment of very recently developed atrial fibrillation as well as for atrial fibrillation during two months. The first aim of this study is to demonstrate that ketodoxapram can slow down the atrial fibrillation and treat experimentally induced atrial fibrillation in the horse. Using an implanted pacemaker, we will induce atrial fibrillation during 48 hours. By acquiring minimally invasive atrial biopsies using a forceps introduced through the jugular vein in the standing horse, we will evaluate whether this results in a higher expression of the TASK-1 channels.

Next, we will evaluate whether administration of ketodoxapram will result in cardioversion to normal sinus rhythm. We will compare the ketodoxapram treatment to a placebo treatment. In addition, we will monitor different clinical parameters such as heart rate and respiration before and after administration of ketodoxapram (compared to placebo),

and evaluate the ketodoxapram levels in the blood. The second aim of this study is to use ketodoxapram to treat horses with chronic experimentally induced atrial fibrillation (2 months). We hypothesize that ketodoxapram administration will slow down the atrial fibrillation, and will convert the horses to normal sinus rhythm. Our ultimate goal is to demonstrate that ketodoxapram is a safe and effective treatment option for horses with atrial fibrillation. Ketodoxapram may become the method of choice for pharmacological treatment of horses with atrial fibrillation.

Importance to the Equine Industry: A novel treatment option for atrial fibrillation is important for the equine industry, especially the sports horse industry of all disciplines (racing, jumping, eventing, dressage,...). Atrial fibrillation often results in decreased sports performance and potentially collapse or even sudden cardiac death. Cardiac disease is the third most common cause for poor performance, and atrial fibrillation is seen as the most common pathological arrhythmia causing performance loss in sport horses. Horses with atrial fibrillation that need to perform at high levels, have abnormally elevated heart rates during exercise or show additional arrhythmias should undergo cardioversion.

In addition, prompt treatment after the initiation of atrial fibrillation is important to prevent atrial remodeling. Atrial remodeling stabilizes the arrhythmia and makes it even more difficult to treat. At the Faculty of Veterinary Medicine in Ghent, horses are routinely treated with transvenous electrical cardioversion, with a success rate of about 95%. However, this treatment can only be performed in highly specialized centers and is not available in every country. The other option is medical treatment. Traditionally, quinidine sulphate is used in horses with atrial fibrillation. However, the success rate is lower (60-80% depending on the type of horse treated) and this medication is increasingly difficult to obtain in many countries: indeed, the product is disappearing from the market because of frequent side effects in humans and animals. Other available products give conversion in 50% of cases at most.

Moreover, serious side effects are described for each of these products. Therefore, a novel safe and effective treatment for atrial fibrillation is urgently needed. The aim of this study is to evaluate a new drug, ketodoxapram, for the treatment of atrial fibrillation. In the future, ketodoxapram may become the treatment of choice for horses with acute or chronic atrial fibrillation.

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