First Human and Veterinary Crossover Symposium on Aldosterone

The efficacy of Spironolactone in human and canine patients suffering from cardiovascular diseases

**SUMMARY:**
- Introduction
- The use of Mineralocorticoid Receptor antagonists in man
- Efficacy of Spironolactone in dogs
- Principles of survival analysis illustrated by CEVA’s Spironolactone trials
- References

**Keywords:** Canine, Clinical benefits, Heart Failure, Human patients, Mineralocorticoid receptor antagonists, Spironolactone, Survival analysis.

The effects of aldosterone, a mineralocorticoid hormone, on the progression of heart failure was the focus of a recent symposium, hosted by CEVA Santé Animale in Bordeaux, France, which brought together veterinary and medical cardiologists, as well as eminent scientists, from around the world. The result was an informative and thought-provoking meeting, mixing state-of-the-art science with the most recent clinical developments in man and animals.

This CardioNews issue reports on the clinical benefits of Mineralocorticoid Receptor (MR) antagonists, such as spironolactone, when treating heart failure in both human and veterinary patients. The key questions raised by the delegates are presented at the end.

**LECTURERS:**
- **Bertram Pitt**
  MD, Professor of Medicine Emeritus, University of Michigan, School of Medicine, Ann Arbor, Michigan, USA.
- **Claudio Bussadori**
  DVM, MD, DipECVIM (Cardiology), PhD, Director of Clinica Veterinaria Gran Sasso, Researcher at paediatric cardiology department of S.Donato Hospital S.Donato Milanese, Milan, Italy.
- **John Martin Bland**
  PhD, MSc, DIC, ARCS, FSS, Hon. MCRP, Professor of Health Statistics, Dept. of Health Sciences, University of York, York, England.

**Introduction**

The clinical benefits of Mineralocorticoid Receptor (MR) antagonists (such as spironolactone and eplerenone) were outlined by Professor Bertram Pitt from the University of Michigan School of Medicine who discussed two large human studies assessing the efficacy of MR antagonists in human cardiac patients. The spotlight then switched to veterinary experiences with spironolactone and Dr Claudio Bussadori from Milan - dually qualified as a veterinary surgeon and medical doctor - described a large clinical trial where the efficacy of spironolactone in treating Myxomatous Mitral Valve Disease (MMVD) in dogs was assessed. Using data from the spironolactone efficacy study described by Dr Bussadori, Professor John Martin Bland, from the Department of Health Statistics at the University of York, then explained how survival statistics are calculated, what they mean in every day terms and the significance of the results achieved.
I - The use of Mineralocorticoid Receptor antagonists in man

1 - Mineralocorticoid Receptor antagonists: a class 1 indication for the treatment of heart failure in human patients

Mineralocorticoid Receptor (MR) blockade is emerging as an important component in the therapeutic approach to heart failure in human medicine. This is following two large trials, called the RALES and EPHESUS trials, for which the speaker Professor Pitt was the lead author.

In the RALES trial, 1663 patients with chronic severe heart failure were enrolled (NYHA class III-IV) and received either spironolactone or placebo, in addition to standard therapy (which included an ACE Inhibitor, furosemide +/- digoxin). The results were dramatic, with a 31% reduction in the risk of mortality from cardiac causes in the spironolactone group (see figure 1). Patients treated with spironolactone also had a lower hospitalisation rate and a significant improvement in heart failure symptoms.

In fact the results were so positive that, for ethical reasons, the trial was discontinued after 24 months because an interim analysis determined that spironolactone was efficacious and therefore all patients in the trial should be receiving the drug.

The EPHESUS trial, also carried out and presented by Professor Pitt, looked at 6642 people with heart failure following myocardial infarction who were randomised to either receive the aldosterone antagonist eplerenone or placebo in addition to other standard therapies, which included Angiotensin Converting Enzyme (ACE) inhibitors or angiotensin receptors blockers, beta-blockers, aspirin and furosemide. In this study, there was a statistically significant 15% reduction in the risk of mortality and a 23% reduction in the hospitalisation episodes caused by heart failure.

As a result of these human studies, Professor Pitt explained that MR antagonists now have a class 1 indication in both European and US guidelines for the treatment of heart failure in people, which means that the benefits of therapy outweigh the risks and treatment should be administered. He also stressed that “the clinical benefits of spironolactone and eplerenone are greater the sooner that therapy is started”. These
benefits appear to be in addition to standard therapy, including an ACE inhibitor.

It was traditionally thought that by blocking ACE, you would remove the deleterious effects of aldosterone but Professor Pitt explained that this is not the case due to alternative (chymase) pathways for angiotensin II synthesis and the fact that, in addition to angiotensin II, there are other stimuli for aldosterone production. Professor Pitt also explained that the clinical benefits of MR blockade are due to the harmful consequences of MR activation. These include an increased myocardial calcium channel expression and electrical remodelling (which increases the propensity towards sudden death and arrhythmias) as well as ventricular inflammation, fibrosis and hypertrophy (which speeds up the progression of heart failure).

II - Efficacy of Spironolactone in dogs

1 - Presentation of the multicentre clinical trials in dogs

In addition to human patients, aldosterone is also known to be involved in the pathophysiology of canine heart failure. Dr Bussadori presented the findings from a recently published clinical trial which tested the efficacy of spironolactone in dogs with myxomatous mitral valve disease (MMVD). A total of 212 dogs with MMVD from 32 veterinary practices in France, Germany, Belgium and Italy were enrolled into this prospective, double-blinded, placebo-controlled study.

To be included, dogs must have presented with at least one of cough, dyspnoea or syncope, and at least one of reduced activity, decreased mobility or altered demeanour.

The study was divided into two consecutive stages. In the first stage, dogs were recruited into two separate studies; one 2 month study, where furosemide was mandatory at inclusion, and one 3 month study, where furosemide was not allowed at inclusion but could be introduced after 5 days. All dogs received an ACE inhibitor and either spironolactone (at a dose of 2mg/kg once daily with food) or placebo.

2 - Ongoing clinical trials in human patients and future indications

Currently two large studies are underway examining the efficacy of eplerenone in human patients with mild (NYHA class II) heart failure (the EMPHASIS-HF trial) and spironolactone in patients with diastolic heart failure (the TOPCAT trial).

To conclude, Professor Pitt postulated that, in view of the finding that MR blockade prevents myocardial and vascular fibrosis and hypertrophy, MR antagonists will play an increasingly important role in the treatment of the entire spectrum of heart failure in man.
Other authorised treatments included digoxin and L-carnitine. During the follow-up, veterinary surgeons were free to change the dose rate, initiate to terminate furosemide dosing according to their clinical judgement. Pimobendan was not permitted as it was not registered in all European countries at the time of the study. The second stage was a 12 month study involving dogs that had completed either of the first two studies, where they continued to receive the same trial treatments.

The primary end points were cardiac-related death, euthanasia due to mitral regurgitation or severe worsening of mitral regurgitation, which was defined as the need for an unauthorised cardiac treatment or to increase the dose of furosemide over 10 mg/kg/day to prevent life-threatening congestive heart failure.

2 - Results: a significant benefit on survival time

Of the 212 dogs enrolled, 179 completed the initial study and 123 continued into the 12 month extended study; the owners of the other 56 dogs were reluctant to commit to the re-examinations in this phase. In the spironolactone and control groups, 34% and 40% completed the entire 15-month study period and end points were reached in 10.8% and 25.5% of dogs in the two groups, respectively (Fischer’s exact test, p=0.0046). This represents a highly significant 55% reduction in the risk of mortality or worsening of disease in dogs treated with spironolactone (hazard ratio = 0.45, p = 0.017).

When only mortality was considered, there was an even more significant 69% reduction in the risk of mortality (hazard ratio = 0.31, p = 0.0071).

This study unequivocally demonstrates that the addition of spironolactone to conventional cardiac therapies significantly and substantially reduces the risk of cardiac morbidity and mortality in dogs with MMVD. Dr Bussadori concluded that the benefit cannot be explained by the mild diuretic effect of the drug. Rather, he suggested, spironolactone counteracts the intramyocardial arterial changes and replacement fibrosis that have recently been described in dogs with MMVD. He concluded that “If the trial would have concerned human patients, we would have put everyone on spironolactone halfway through the trial for ethical reasons.”
III - Principles of survival analysis illustrated by CEVA’s Spironolactone trials

In the next presentation Professor Martin Bland, from the Department of Health Statistics at the University of York, described how survival statistics were created and how to interpret the results. In the CEVA clinical trials, the end-point (or event) was death or euthanasia due to heart failure or severe worsening of mitral regurgitation and the time to death or euthanasia was recorded in days. Some dogs were censored because they were still alive at the end of the 15 month trial, were withdrawn from the trial at the owners request (usually because they no longer wished to have the regular assessments) or because some dogs died from causes unrelated to heart failure. These “censored” cases can be taken into account by calculating the survival probability throughout the study, which forms the basis of the Kaplan-Meier survival curve (see figures 1 and 2).

At the start of a survival study, the survival probability is always 1, which means all of the patients are alive. In the spironolactone study, there were 110 dogs in the control group at the start of the study. One dog died from heart failure on day 6, meaning there were 109 dogs still surviving. The survival probability would now be 109/110, i.e. 0.9909. On day 7, another dog was censored, i.e. left the study or died for a reason other than heart failure. The survival probability was still 0.9909 but the number of dogs in the study was now reduced to 108. On day 8, another dog died from heart failure. The survival probability was now 107/108, i.e. 0.9907. The total probability of surviving beyond day 8 was therefore 0.9909 multiplied by 0.9907, i.e. 0.9817. In this way, survival probabilities can be calculated throughout the study and Kaplan Meier survival curves created (see figures 1 and 2). Days when there are no events and no censorings are not recorded as these do not alter the proportion surviving or the number at risk. For these periods, the Kaplan-Meier survival curve therefore appears flat.

In the case of the spironolactone trial (figure 2), the Kaplan-Meier survival curve clearly showed that survival was better in the spironolactone-treated dogs but how do you know if the difference is significant? This is assessed by using the logrank test, which calculates the number of expected deaths in each group if the chance of experiencing an event was the same for both groups. For the spironolactone trial data, we would expect 13.11 deaths in the spironolactone group and 14.89 deaths in the control group. In actual fact, there were 6 deaths in the spironolactone group and 22 deaths in the control group. The probability of a difference this large occurring by chance is 0.7%, i.e. would only happen in 7 out of 1000 samples. This is highly statistically significant. The logrank test gives the significance of a treatment effect but does not produce an estimate of the size of the difference between treatment groups.

Professor Bland explained that this is best carried out by looking at the hazard ratio, which is a measure of the chance that a member of any population will have an event at any given time.
If the risk of an event is the same in the placebo and treatment group, then the hazard ratio is 1.0.

The lower the hazard ratio, then the greater the difference between the two groups. For the spironolactone study, the hazard ratio was 0.31, which represents a 69% reduction in the risk of mortality in the spironolactone group or, put another way, the risk of death in the spironolactone group at any given time was one third of that in the control group.

Professor Bland put this result in perspective by saying that in the Lancet, one of the most highly cited medical journals, 10 studies quoted hazard ratios in the first 3 months of 2007 with an average hazard ratio of 0.7, i.e. a 30% reduction in the risk of an event happening.

A hazard ratio of 0.31 is therefore very large difference in a clinical trial and he concluded by saying that spironolactone for heart failure in dogs is an “unusually effective treatment that clearly prolongs life”.

**Conclusion**

This edition of Cardionews highlights the benefits of adding spironolactone to both human and veterinary heart failure patients. During the seminar, Professor Pitt, the lead author of two large human trials (RALES and EPHEBUS), clearly explained how Mineralocorticoid Receptor antagonists have dramatically improved the outcome for human cardiac patients. Dr Bussadori then reviewed the published clinical trial work in dogs, where an even greater benefit of adding spironolactone to conventional treatment in dogs was demonstrated.

Finally Professor Bland explained how the survival statistics were calculated and how they demonstrate that spironolactone is an “unusually effective treatment that clearly prolongs life”. These results support the use of spironolactone as an essential part of first line therapy for the treatment of heart failure cause by mitral valve disease in dogs.
Question 1 (Delegate) - Comparing the number of people or animals in heart failure with the number at risk or in early stages, is there an argument for instituting treatment very early in the disease?

Answer (B. Pitt) - Our goal should be to prevent heart failure in humans, but it will take 10-15,000 patients and several hundred million dollars to perform the requisite clinical studies, and so it is unlikely that this research will be done.

Question 2 (Chair) - Is there any difference between eplerenone and spironolactone?

Answer (B. Pitt) - I have asked Pfizer many times to do a comparison. There have been a few clinical comparisons and lots of experimental work. These show that their efficacy is similar.

Question 3 (Delegate) - How do you prove the diuretic effect of spironolactone? Is there any evidence of weight loss or oedema reduction?

Answer (C. Bussadori) - In the canine trial, there was no direct evidence of the diuretic effect, although we were not looking specifically at this. In reality it is impossible to differentiate in this study between the effects of furosemide and spironolactone on diuresis.

Answer (L. Baduel) - We found no difference in the mean furosemide doses used between the two groups.

Question 4 (Delegate) - How can we keep confidence in trial, such as this, where there is a high censor rate?

Answer (J. M. Bland) - Many censorings were because owners did not wish the dog to continue from the first to the second stage of the trial.

The proportion of dogs censored were very similar in the two groups and survival curves were drawn considering the censored data. The efficacy of spironolactone was demonstrated comparing these two curves. The number of censorings in the spironolactone study was not, in my experience, unreasonable.

Photo 1:
The presentation of Ceva’s Spironolactone clinical trials allowed the delegates to ask their different questions on the clinical and statistical aspects as well. From left to right: Mark A. Oyama, Laure Baduel, John M. Bland, Claudio Bussadori.
References


6. A comparison of outcomes in patients in New York Heart Association (NYHA) Class II Heart Failure when treated with Eplerenone or placebo in addition to standard Heart Failure medicines. Available at ClinicalTrials.gov. Emphasis –HF. NCT00232180

7. Aldosterone antagonist therapy for adults with heart failure and preserved systolic function. Available at ClinicalTrials.gov. TOPCAT. NCT00094302