Is treatment with pimobendan associated with an increased risk of arrhythmias in dogs with heart disease?

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**Clinical scenario**
Pimobendan is a positive inotrope and balanced vasodilator via its actions as a calcium sensitiser and phosphodiesterase III inhibitor, respectively. There is strong evidence for its use in the treatment of dogs with congestive heart failure (CHF), with multiple clinical trials demonstrating a resultant increase in survival time. However, the use of pimobendan for treatment of heart disease in people has been associated with increased risk of arrhythmias. This effect is attributed to the racemic nature of pimobendan resulting in D and L chiral enantiomers, with the L-optical isomer having a significantly greater calcium sensitizing effect. There is limited data available regarding any effect of treatment with pimobendan on the risk of arrhythmias in dogs. The aim of this article is to analyse the available data to determine whether evidenced-based conclusions can be drawn.

**The question**
In [dogs with cardiac disease] does treatment with [pimobendan] compared to [alternative treatments OR placebo] lead to [increased risk of arrhythmias]?

**Search strategy**
The search strategy is available as a supplement to this article on Vet Record's website at http://veterinaryrecord.bmj.com/content/183/22/693

**Search outcome**
- Ten papers found in Medline search
- One was excluded because it was a duplicate
- Eight were excluded because they did not answer the question
- One relevant paper was identified from Medline
- Eighteen papers found in CAB search
- Sixteen were excluded as they did not answer the question
- Two relevant papers were identified from CAB Abstracts
- Four papers were identified from other sources

**Summary of evidence**

**Paper 1:** Effect of pimobendan on the incidence of arrhythmias in small breed dogs with myxomatous mitral valve degeneration (MMVD)

**Patient group:** Eight client-owned small breed dogs (<15 kg) with CHF due to MMVD. Four dogs received placebo and four received pimobendan.

**Study type:** Prospective double-blind randomised placebo-controlled crossover study.

**Outcomes:** Two weeks after administration of the placebo or pimobendan, average heart rate, type and incidence of arrhythmia, determined using 24-hour Holter ECG analysis, was compared to baseline data. A quality of life questionnaire was completed and sleeping respiration rates recorded by owners at baseline and two weeks after drug administration.

**Key results:** Quality of life scores calculated using owner questionnaires were significantly improved following administration of both placebo (P=0.021) and pimobendan (P=0.001). No significant differences were identified in the type or incidence of arrhythmias. Average heart rate in dogs that received pimobendan was significantly lower than baseline (P<0.001), as was sleeping respiratory rate (P=0.004), which was also significantly different from those that received the placebo (P=0.045).

**Study weaknesses:** While key results were significantly different between treatment groups it must be noted that the small study size resulted in the study not being underpowered for some tests. The effect of pimobendan was also only assessed in small breed dogs and so conclusions can only be applied to this subject group. Furthermore, only dogs with stable, medically controlled CHF due to MMVD were included, and so it could not be concluded that treatment with pimobendan would not result in arrhythmias in earlier stages of MMVD or in other cardiac diseases. CHF was identified on thoracic radiography which, although generally agreed as the gold standard diagnostic test in veterinary medicine, can be subjective. Additionally, heart rate and rhythm were only recorded for 24 hours using the Holter ECG monitor, which might be insufficient to detect all arrhythmias that may be present. Finally, administration of pimobendan for two weeks may not be long enough for the drug to have a proarrhythmic effect.

**Paper 2:** Effects of the positive inotropic agents milrinone and pimobendan on the development of lethal ischaemic arrhythmias in conscious dogs with recent myocardial infarction

**Patient group:** Thirty-six male or female mixed-breed dogs with experimentally induced myocardial infarction.

Potential study animals underwent electrical stimulation to assess for a predisposition to develop arrhythmias; only unresponsive animals were selected for the study as they were considered ‘low risk’ for the development of subsequent lethal ischaemic arrhythmias. Of the animals deemed ‘low risk’ and therefore entered into the investigation,
10 dogs received 200 µg/kg/hour of milrinone administered via constant rate infusion for six hours, nine received 300 µg/kg pimobendan administered intravenously over 20 minutes, and 12 received a placebo solution (six received 50 per cent polyethylene glycol-200 in 0.9 per cent saline and six received just 0.9 per cent saline).

**Study type:** Prospective, randomised, placebo-controlled study.

**Outcomes:** Electrophysiological testing and programmed ventricular stimulation were undertaken at 30 minutes after pimobendan and vehicle administration and two hours after milrinone administration to allow for the development of equivalent inotropic responses in the two groups. The parameters measured included: ECG intervals, minimum voltage required to produce a conducted ventricular impulse, and incidence of ischaemic mortality at 24 hours following development of posterolateral myocardial ischaemia.

**Key results:** Administration of pimobendan after a myocardial infarction event resulted in significant shortening of PR (P=0.01) and QIC intervals (P=0.05), as well as generalised shortening of refractory periods (P values ranged from 0.01 to 0.06 depending on the exact measurement site). All placebo- and pimobendan-treated animals remained unresponsive to programmed ventricular stimulation at all time points. However, one pimobendan-treated animal was excluded due to the postdrug appearance of spontaneous ventricular ectopy. No spontaneous or provoked ventricular ectopy was observed in the remaining pimobendan-treated animals. Pimobendan administration resulted in a significant increase in the incidence of sudden ischaemic ventricular fibrillation; however, incidence of ischaemic mortality at 24 hours was not significant (P=0.083) when compared to the low risk control group.

**Study weaknesses:** This study was carried out on dogs with experimentally induced myocardial infarction, a condition rarely seen in dogs. Furthermore, a dose of 300 µg/kg pimobendan administered intravenously over 20 minutes and a 200 µg/kg/hour dose of milrinone administered via continuous intravenous infusion for six hours were used. These regimes were selected because of their ability to produce a significant and sustained increase in cardiac inotropic status; there was no attempt to recreate therapeutic dosing schedules, 0.15 mg pimobendan/kg bodyweight injectable solution, used for clinical canine heart failure patients.

**Paper 3:** Effect of pimobendan or benazepril hydrochloride on survival times in dogs with congestive heart failure caused by naturally occurring myxomatous mitral valve disease: the QUEST study

**Patient group:** Two-hundred-and-sixty client-owned dogs recruited from 28 centres in Europe, Canada, and Australia were included in the study.

**Study type:** Prospective, multicentre, single-blinded, positive-controlled study.

**Outcomes:** The primary end point was a composite of cardiac death, euthanasia as a result of heart failure or treatment failure. The onset of arrhythmias was assessed at one, three, six, nine, 12, 15 and 18 months using ECG.

**Key results:** The time to end point was 267 days for pimobendan and 140 days for benazepril (hazard ratio 0.688, 95 per cent confidence intervals [CI] 0.516 to 0.916, P=0.0099). This benefit persisted after adjustment for baseline variables. There was no difference in the onset of arrhythmias between the two treatment groups.

**Study weaknesses:** Only dogs with CHF as a result of MMVD were included. The primary end point was a composite of three possible outcomes (only two resulting in death), the third (treatment failure) lacks the incontrovertible nature of death and is yet to be validated as a good surrogate for survival; however, the study outlines what was predefined as treatment failure. Treatment failure was used as a surrogate in 20 pimobendan and 27 benazepril dogs. Lack of double blinding meant that owners were aware of the medication used. Defining the cause of death as cardiac or non-cardiac in an aging population is problematic due to comorbidity. Study population had a larger proportion of Cavalier King Charles spaniels and dachshunds than previous large trials. The primary parameter assessed was treatment efficacy; therefore, the study was not designed specifically to detect arrhythmias, although ECGs were performed at multiple time points throughout the study and onset of arrhythmias recorded.

**Paper 4:** Efficacy of pimobendan in the prevention of congestive heart failure or sudden death in doberman pinschers with preclinical dilated cardiomyopathy (DCM) (The Protect Study)

**Patient group:** Seventy-six client-owned dobermans at 10 centres in the UK and North America were included in the study.

**Study type:** Randomised, double blinded, placebo-controlled, parallel-group multi-centre study.

**Outcomes:** Primary end point was composite of onset of CHF or sudden death, secondary end point was death by any cause.

**Key results:** No significant difference between the proportion of dogs reaching the end point in the pimobendan versus the placebo group (P=0.1). Median time to primary end point was significantly longer in pimobendan group (718 days, interquartile range [IQR] 151 to 641 days) v the placebo group (441 days, IQR 151 to 641 days) (P=0.008). Median survival time was also significantly longer in pimobendan group (623 days, IQR 491 to 1531 days) v the placebo group (466 days, IQR 236 to 710 days) (P=0.034). The primary end point was reached earlier in dogs with higher heart rates and those with greater than four ventricular premature complexes on a three minute ECG. No increased risk of pro-arrhythmia or sudden death was associated with use of pimobendan (P=0.30).

**Study weaknesses:** Only dilated cardiomyopathy in dobermans was studied. A significant number of dobermans with preclinical DCM develop arrhythmias, which may result in sudden death. Dogs with arrhythmias before treatment were noted in the study but not excluded. The study protocol was amended during recruitment to include hypothyroid dogs. Antiarrhythmic therapy was permitted if dogs developed ventricular arrhythmias during the trial, and these dogs remained in the study. Physical examinations were only performed every six months.

**Paper 5:** Effect of pimobendan in dogs with preclinical myxomatous mitral valve disease and cardiomegaly: EPIC study

**Patient group:** Three-hundred-and-sixty client-owned dogs with MMVD with left atrial-to-aortic ratio over 1.6, normalised left ventricular internal diameter in diastole over 1.7, and vertebral heart sum over 10.5.

**Study type:** Prospective, randomised, placebo-controlled, double blinded, multicentre clinical trial.

**Outcomes:** Time to a composite of the onset of CHF, cardiac-related death, or euthanasia.

**Key results:** Median time to primary endpoint was 1228 days in the pimobendan group and 277 days in the placebo group (P=0.0038). Hazard ratio for pimobendan group was 0.64 compared with the placebo group (P=0.0002). There was no difference in adverse events between treatment groups (P=0.82).
Study weaknesses: This study only assessed the effects of pimobendan in dogs with MMVD. Dogs under six-years-old and those under 4.1 kg and over 15 kg were excluded. While adverse events were noted and reported the study did not specifically investigate the incidence of arrhythmias; therefore it is possible that their presence were missed. Additionally, the summary of adverse events reported does not specifically list ‘arrhythmia’ and instead lists ‘tachycardia’ and further, a large proportion of the adverse events are categorised as ‘other’ (124/196).

Paper 6: Longitudinal analysis of quality of life, clinical, radiographic, echocardiographic, and laboratory variables in dogs with preclinical myxomatous mitral valve disease receiving pimobendan or placebo: the EPIC study

Patient group: Three hundred and fifty-four dogs with MMVD and cardiomegaly.

Study type: Prospective, double-blinded study with dogs randomised (ratio 1:1) to pimobendan or placebo.

Outcomes: Clinical, laboratory, and heart size variables in both groups were measured and compared at different time points and over the study duration. Relationships between short-term changes in echocardiographic variables and time to CHF and cardiac-related death (CRD) were explored.

Key results: Heart size reduced in the pimobendan group compared to placebo (P<0.0001); this reduction was associated with an increased time to CHF and CRD; hazard ratio for a 0.1 increase in normalised myocardial infarction, a proarrhythmic model, making it impossible to draw accurate comparisons to non-ischaemic conditions such as MMVD. Furthermore, dogs in this study were administered pimobendan doses chosen to induce increased cardiac inotropic status. Therefore, it can be concluded that the finding of increased ventricular fibrillation in this study is not clinically relevant. The QUEST, PROTECT and both EPIC studies were the largest and best designed. While none specifically aimed to collect data on occurrence of arrhythmias, the QUEST study found no increase in the onset of arrhythmia and the PROTECT study found no increased risk of proarrhythmia. Disappointingly, neither EPIC study specifically reports arrhythmias as an adverse event; however, the first does report no overall difference in adverse events between the two study groups.

The studies varied in quality and strength of evidence. Only two studies specifically investigated arrhythmia, one very small and the other carried out in an experimentally induced proarrhythmic disease model using non-therapeutic doses of pimobendan. The much larger EPIC study reported equal incidence of adverse events while the PROTECT study found no increase in risk of proarrhythmia. Although neither EPIC study specifically reports arrhythmias as an adverse event; however, the first does report no overall difference in adverse events between the two study groups.

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Bottom line
To date there is no evidence to suggest pimobendan is associated with an increased risk of arrhythmias in dogs.

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