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Tiletamine–Zolazepam and Xylazine is a Potent Cardiodepressive Combination: a Case Report

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Intramuscular injection of tiletamine–zolazepam and xylazine is commonly used as a preanesthetic for veterinary surgical procedures and for short-term restraint. However, this combination can have marked cardiodepressive and hypothermic effects that persist for hours to days. Here we present a case report of these effects in a swine heart failure model.

Abbreviations: dP/dt, first derivative of the blood pressure; ppm, paces per minute; Tau, left ventricular relaxation time constant; Vmax, maximal upstroke velocity

Intramuscular injection of tiletamine–zolazepam and xylazine is commonly used as a preanesthetic for veterinary surgical procedures and to produce short-term restraint.[5-7] This drug combination is popular because of its smooth induction and recovery profile and its low volume-to-dose ratio. However, although cardiodepression is often mentioned as a potential side effect,[4,11,12] specific supporting documentation is difficult to find in the literature. Here we report a case in which tiletamine–zolazepam–xylazine caused marked cardiodepressive and hypothermic effects in a swine heart failure model.

Materials and Methods

The present study used a rapid-pacing model of heart failure.[1,2,10,13] A single Yucatan minipig (*Sus scrofa domestica*; female, 43.4 kg, certified specific-pathogen–free; S and S Farms, MI) was used in this study. The institutional animal care and use committee of the research facility reviewed and approved the study protocol. The animal was housed in a 2.8-m^2 enclosure with free water access via a spout and was treated and cared for in accordance with the *Guide for the Care and Use of Laboratory Animals*.[8]

The pig received the combination of tiletamine–zolazepam (4.4 mg/kg; Telazol, Fort Dodge Animal Health, Fort Dodge, IA) plus xylazine (2.2 mg/kg; Phoenix Scientific, St Joseph, MO) intramuscularly as a preanesthetic agent. The pig was intubated and anesthetized with isoflurane (2%) and oxygen (1.6 l/min) for the duration of the device implant procedure.

After the placement of an arterial line in the right groin area, the heart was exposed through a partial median sternotomy for placement of left ventricular epicardial pacing leads and a left ventricular pressure sensor (LVP-1000, Data Sciences International, St Paul, MN). Additional pacing leads were placed endocardially in the right atrium and right ventricular apex. The pacing leads were connected to a pacemaker (Stratos LV, Biotronik, Berlin, Germany), which was placed in a subcutaneous pocket in the right supraclavicular area. The arterial line was removed, and all incisions were closed. Before extubation, the pig was medicated with penicillin G (600,000 U total; Bicillin) and buprenorphine (0.3 mg).

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Once weekly thereafter, the pig was medicated with the tiletamine–zolazepam–xylazine combination and returned to the laboratory for follow-up exams, including data retrieval from the pacemaker, echocardiogram, and chest fluoroscopic exam. Data from the pressure sensor were measured continuously for a 4-min period every hour for the duration of the study (10 wk) and was telemetered to a computer base station for storage and analysis.

The pressure sensor directly measures the left ventricular pressure and core body temperature. From the acquired measurements, additional parameters are derived, including the systolic, diastolic, and mean pressures; heart rate; the first derivative of the blood pressure (dP/dt); maximal upstroke velocity (Vmax), which is a measure of the contractility of the heart that is unaffected by loading; and Tau, which is defined as the ventricular relaxation time constant from minimum dP/dt to the point where the pressure has dropped 66% of the distance from systolic to diastolic pressure. A prolonged Tau is an indication of diastolic dysfunction. These hourly measurements provided a unique opportunity to observe the effects of the medications on cardiac performance during baseline, heart failure, and heart failure recovery.

Figure 1 shows an overview of the phases, and major milestones, of the study. After stabilization, the pacing rate was increased gradually over 3 d to 240 paces per minute (ppm) to induce heart failure. During this phase, the pacing rate was decreased over 3 min to a subintrinsic rate of 60 ppm prior to each hourly measurement. After each measurement series was completed, the pacing rate resumed at 240 ppm. At the onset of the recovery phase, the pacing rate was gradually decreased over 3 d back to 60 ppm (subintrinsic).

Results

Figure 2 shows trends of the heart rate, left ventricular systolic pressure, Tau, core temperature, and Vmax recorded by the pressure sensor system over the full 70 d of the study. Coincident with the administration of tiletamine–zolazepam–xylazine as a restraint agent during the weekly follow-ups, all of these parameters demonstrated marked perturbations, indicating cardiodepression (decreased heart rate, Vmax, and left ventricular systolic pressure, and an increase of the Tau measurement) and hypothermia.

During the initial stabilization period (until day 28), the

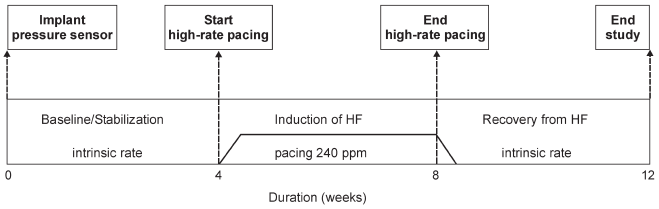

Figure 1. Phases and milestones of the study.

measurements returned to preanesthetic values within 6 to 12 h. During the induction of heart failure (day 28 to day 56), the time to recover increased to 24 to 72 h. The prolongation of the recovery time shows the additional effect of the compromised cardiovascular system due to the high-rate pacing. After high-rate pacing ceased, the time for the measurements to return to the preanesthetic baseline decreased to approximately 12 h, comparable to the recovery time during the initial stabilization phase.

Discussion

Despite the recommended use of the combination of tiletamine–zolazepam–xylazine in veterinary applications as a preanesthetic and restraint agent,[5-7] acute, short-term studies[4-6] have reported decreases in heart rate and body temperature. In fact, the package insert for Telazol[3] (Fort Dodge) warns of possible myocardial depression; the package insert for Xylazine[9] (Phoenix Scientific) warns of bradycardia and partial atrioventricular block and cautions against its use in the setting of severe pathologic heart disease. To our knowledge, this report is the first to describe the long-term effects of tiletamine–zolazepam–xylazine in a chronic setting rather than a short-term observation.

In the reported case, tiletamine–zolazepam–xylazine was used as a preanesthetic prior to surgery and then weekly thereafter for short-term restraint for noninvasive follow-up studies. The data from the implantable left-ventricular pressure monitor demonstrated the cardiodepressive and hypothermic effects of the tiletamine–zolazepam–xylazine combination. The cardiodepressive effects were apparent even when the animal was not compromised cardiovascularly and were exacerbated during heart failure (Figure 2).

The findings discussed in this case report were incidental to the study but were sufficient to cause us to change the preanesthetic–sedative protocol to ketamine (33 mg/kg intramuscularly) and acepromazine (1.1 mg/kg intramuscularly) as a preanesthetic and midazolam (500 µg/kg intramuscularly) for sedation for the remainder of the study. As a result, none of the adverse effects seen with tiletamine–zolazepam–xylazine occurred. However, whether the combination or dosage (or both) of tiletamine-zolazepam, and xylazine produces the undesirable effects or whether the effects are attributable to one agent in the combination is not known.

The current case study demonstrates that the combination of tiletamine–zolazepam and xylazine produces marked depression of cardiac function and core body temperature in a model of heart failure in swine and should therefore be avoided in the setting of cardiovascular studies involving swine.

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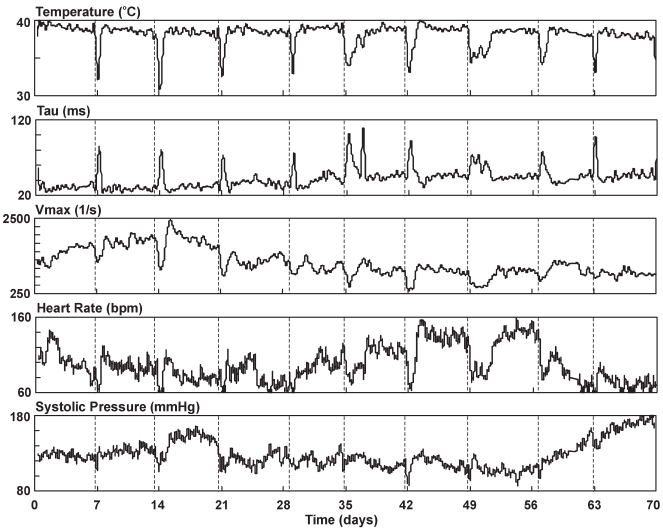

Figure 2. Trends of the parameters measured by using the pressure sensor. The dashed vertical lines indicate administration of the tiletamine–zolazepam–xylazine combination. The dips and peaks that follow are the subsequent effects of the drugs.

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