



NOTE

Internal Medicine

Long term effects of cilostazol in a dog with sick sinus syndrome

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ABSTRACT. Sick sinus syndrome (SSS) is a type of bradyarrhythmia that can lead to syncope. Cilostazol has been reported to be an effective treatment for human patients with SSS and other bradyarrhythmias. This report describes the successful long-term treatment with cilostazol in a dog with SSS. A nine-year old intact male Miniature Schnauzer presented with a history of syncopal episodes and unsteady gait. After cilostazol treatment, the total heart rate (HR), mean HR, and frequency of premature ventricular contractions (PVCs) increased, while the maximum HR and maximum pause time decreased. Additionally, the number of syncopal episodes decreased. The dog died suddenly, 1,418 days after the start of cilostazol treatment. Cilostazol may be a useful therapeutic agent in canines with SSS.

KEY WORDS: cilostazol, dog, sick sinus syndrome

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Sick sinus syndrome (SSS) is a term used to describe the clinical signs of sinus node dysfunction. Pacemaker implantation (PMI) and medical therapeutics are used in veterinary medicine to treat patients with SSS [4, 8, 17, 18]. PMI is the preferred treatment for patients with SSS. However, PMI may not be performed in some patients, because of the high cost and the risks of anesthesia and surgery. Several classes of drugs can be useful in treating SSS, including anticholinergic, beta-adrenergic and xanthine derivative medications. However, these agents may be not beneficial for prolonged treatment [8], especially when the patient fails to respond to the atropine test.

Cilostazol is an oral selective phosphodiesterase type III inhibitor, used in Japan as an antiplatelet and antithrombotic agent for patients with peripheral arterial occlusive disease. Cilostazol has positive chronotropic effects and has been used to treat human patients with bradyarrhythmias, such as atrioventricular (AV) block and SSS [2, 9, 10, 12, 15, 19]. Cilostazol has also been reported to have long-term chronotropic effects [5, 9]. The mechanisms of action of cilostazol include vasodilation resulting in a reflex increase in heart rate (HR), improvement of sinus function by suppression of parasympathetic tone, increased blood flow to the sinus node resulting from coronary artery dilatation, and increased sinus node intracellular cyclic adenosine monophosphate [12]. Cilostazol has been reported to increase the heart rate in experimental dogs [14].

We report a case of long-term administration of cilostazol to a dog with symptomatic SSS, in which a chronotropic effect and long-term improvement of clinical signs were observed.

A nine-year-old intact male Miniature Schnauzer, weighing 6.25 kg, was referred to the Ikime Animal Hospital for episodes of syncope and unsteady gait. On physical examination, the mucous membranes were pink, and capillary refill time was less than two seconds. The dog was bright, alert, and responsive. Findings on neurologic examination were normal. Thoracic auscultation revealed a grade 2/6 systolic murmur, with the point of maximum intensity at the left cardiac apex. The cardiac rhythm was irregular, and the HR varied from 66 to 91 beats per min.

Complete blood cell count results were unremarkable. Serum chemistry results revealed a mild increase in serum alanine aminotransferase (ALT: 127 U/l; reference interval: 15–70 U/l) and a mild increase in atrial natriuretic peptide (ANP: 48.6 pg/ml; reference interval: <30 pg/ml) [3].

Thoracic radiographs displayed an increased vertebral heart score (VHS: 11.3; reference interval: 8.5–10.6), with normal lung fields.

The echocardiogram showed mild eccentric left ventricular hypertrophy (left ventricular internal end-diastolic diameter/left ventricular end-systolic internal diameter; LVIDd/ LVIDs: 31.0/17.8 mm), mild mitral regurgitation, sinus arrest and AV block. The

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Fig. 1. The electrocardiogram recording (lead II; 50 mm/sec), obtained from a dog with sick sinus syndrome, showing sinus arrest before treatment with cilostazol.

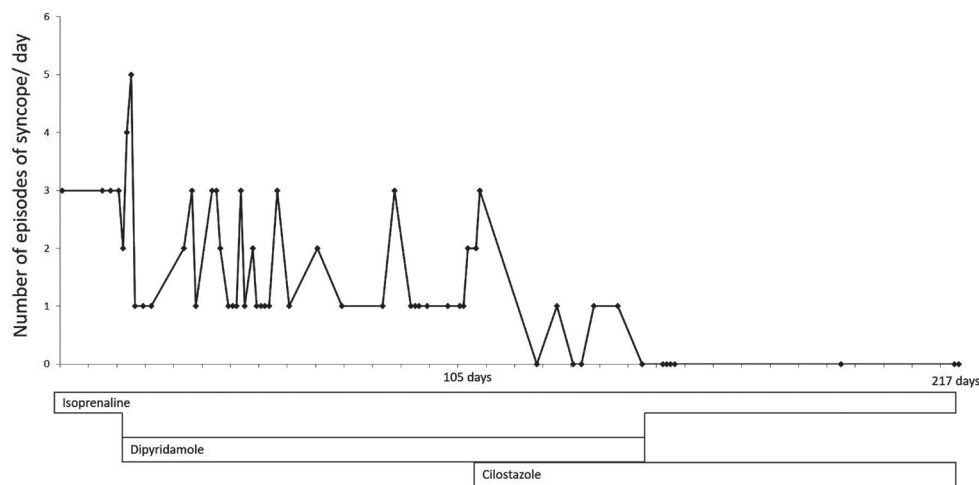


Fig. 2. Number of syncopal episodes recorded by the owner, per day, before and after treatment.

atria and right ventricle were considered within normal limits.

The electrocardiogram (ECG) revealed bradycardia and sinus arrest (Fig. 1). Sinus node function was evaluated by the response to atropine. Atropine was administered (0.04 mg/kg intramuscularly), and the ECG was repeated 30 min after the injection. No heart rate response to atropine was seen (pre HR=86; post HR=78 beats per min). A 24-hr Holter ECG (Quick Corder QR2100, Fukuda M-E Kogyo Inc., Tokyo, Japan) showed sick sinus syndrome and long periods of sinus arrest (Maximum pause: 9,210 msec) (Table 1). Premature atrial contractions, premature ventricular contractions (PVCs) and AV block were also noted. Furthermore, bradyarrhythmias and tachyarrhythmias alternated, resulting in a diagnosis of severe SSS with bradycardia-tachycardia syndrome, Rubenstein type III [13].

Since the owner declined PMI, we attempted medical management of the patient. Prior to beginning treatment, the owner recorded the number of episodes of syncope and collapse (Fig. 2). The dog was prescribed isoprenaline (0.5 mg/kg twice daily PO; Protanol, Kowa Pharmaceutical Co., Ltd., Tokyo, Japan). However, after 7 days of treatment, the number of episodes of syncope had not decreased. The isoprenaline dose was increased to three times per day, and dipyridamole (0.5 mg/kg twice daily PO; Persantine, Boehringer Ingelheim Pharmaceuticals Inc., Tokyo, Japan) was added. After 105 days of treatment, no improvement was seen in the patient's condition. Furthermore, the plasma ANP concentration had increased (137 pg/ml), suggesting a poor clinical response to this treatment.

Therefore, the dog was prescribed cilostazol (10 mg/kg twice daily PO; Pletal, Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan). At 14 days after the start of cilostazol treatment, the patient had decreased number of episodes of syncope (Fig. 2), and the ANP concentration had decreased (46.6 pg/ml). A 24-hr Holter examination was repeated (Table 1). The total HR, mean HR and number of PVCs had increased, while the maximum HR and maximum pause time had decreased. Twenty days after the start of cilostazol,

Table 1. Holter electrocardiogram tracings obtained from a dog with sick sinus syndrome, before and 118 days after starting cilostazol

		Pre	Post
Total QRS		100,078	111,719
	Minimum HR (bpm)	14	22
	Mean HR (bpm)	68	76
	Maximum HR (bpm)	191	175
PVC	singles	204	7,707
	pairs	5	495
	3 or more	2	118
PAC	singles	17,634	12,243
	pairs	4,536	2,724
	3 or more	3,137	3,638
Pause	No of pause (>2.0 msec)	9,036	9,603
	Maximum pause (msec)	9,210	6,360

HR: heart rate, PAC: premature atrial contraction, PVC: premature ventricular contraction.

the owner reported seeing a small amount of bright red blood on the feces. Cilostazol was continued, and the problem resolved within two days. Despite cilostazol therapy, arrhythmias without prolonged sinus arrest persisted. Conventional ECG, radiographic and echocardiographic findings were unchanged at 642 days after beginning cilostazol treatment. The owner reported that episodes of syncope remained decrease. The dog died suddenly, 1,418 days after the onset of cilostazol treatment. The cause of death was not determined.

In our case, PMI was not performed according to the owner's request. Dogs with SSS that do not respond to medical treatment, have adverse side effects, or have bradycardia-tachycardia syndrome generally require a pacemaker [12]. Medical management may increase the risk of worsening the bradycardia-tachycardia syndrome [5]. However, it is reported that median survival time is similar in patients with SSS managed medically compared to those with a pacemaker [17]. In our patient, we did not use atropine and propantheline, since the atropine test was negative. The beta-agonist, isoprenaline, provided slight improvement for a short time in our patient because degree of syncope decreased. However, the therapeutic effect did not persist, likely because of down regulation of the beta-adrenergic receptors. The episodes of syncope were disappeared by cilostazol administration in our case.

Varied clinical results have been seen with the use of cilostazol for human patients with SSS Rubenstein type III [5, 16]. In our canine patient with SSS, Rubenstein type III, we observed positive long-term clinical effects. The total HR, mean HR, and frequency of PVCs increased, while the maximum HR and maximum pause time decreased. Achievement of a normal sinus rate and improvement of AV synchrony did not occur. The increase in HR is likely related to the increased frequency of PVCs. In human patients with AV block, improvement of AV conduction and synchrony is not observed. Both canine and human patients with SSS treated with cilostazol can experience decreased sinus node pause time. Additionally in this case, cardiac preload due to marked bradycardia was improved as a result of the decreased ANP concentration. Cilostazol treatment may be effective and one of the medical therapy options in dogs with SSS, although it may not result in a normal sinus rhythm.

To the best of our knowledge, we report the first case of effective, long-term cilostazol treatment in a dog with SSS. There have been reports of undesirable side effects, including premature beats and atrial fibrillation, associated with long-term cilostazol therapy for human patients [5, 9]. In this case, although the patient exhibited premature beats, atrial fibrillation was not observed. In human patients, cilostazol is used until PMI can be performed and in patients unable to receive a pacemaker [5, 9, 10].

While on cilostazol, the patient had a two-day episode of bloody feces. While it is unclear that the bloody feces resulted from cilostazol, this occurrence suggests that additional therapy with other antithrombotic agents should be used cautiously in dogs.

To determine the dosage, we referenced a study with dogs and case reports of human patients with bradyarrhythmias [1, 2, 6, 7, 9–11, 14, 19]. The effects of both increased HR and decreased blood pressure are concentration-dependent [14]. There is no evidence of cilostazol accumulation from repeated doses (7 days). In addition, at a dose of 3 mg/kg, the time after administration to maximum concentration was 3 hr, and the apparent half-life was 1.6 hr. Thus, administration every 8 to 12 hr is desirable. Based on these factors, we decided to administer a dose of 10 mg/kg every 12 hr.

The patient dog had long-term survival after treatment with cilostazol in this case report. However, the cause of death is unknown because a patient dog have died at home and we could not make a necropsy. It is not clear whether cilostazol treatment is related to sudden death.

In conclusion, Cilostazol could be one of therapeutic agents for dog with SSS. Further studies are needed to confirm efficacy and safety of cilostazol treatment.

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