Mirabegron Toxicosis in Dogs: a Retrospective Study

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Abstract

Mirabegron is a selective *beta* (B)₃ adrenoreceptor agonist marketed for human treatment of an overactive bladder (OAB). It has a wide margin of safety in humans, but in dogs, severe adverse effects have occurred. We sought to determine the effects and outcome of mirabegron toxicosis in dogs. A retrospective review of all calls within the Pet Poison Helpline (PPH), an international animal poison control center, database was performed for mirabegron exposures between 2013 and 2015. Potential ingested doses ranging from 1.31 to 8.3 mg/kg. Many dogs remained asymptomatic and no fatalities occurred in any dogs. The most commonly reported signs were tachycardia and erythema. While mirabegron was found to have a very narrow margin of safety and high toxicity risk to dogs during preclinical trials, effects appear to differ greatly in the nonclinical field environment and further study is needed.

Keywords Dog · Mirabegron · Tachycardia · Cardiotoxicity · Erythema · Salivary gland

Introduction

Beta adrenergic receptors are found throughout the body in the cardiac muscle, urinary bladder, bronchial tree, gastrointestinal tract, salivary glands, sweat glands, and cardiac pacemaker [1]. *Beta*₃ adrenoreceptors were first identified in brown adipose tissue of rats in 1984 and believed to be involved in thermogenesis and lipolysis [2]. They have since been located in the smooth muscle of both the urinary bladder and gastrointestinal tract [3]. In addition, *B*₃ adrenoreceptors are specifically located in skeletal muscle, adipose tissue, and myocardium [4]. Original studies with these receptors also investigated the potential treatment of obesity and diabetes with little success [2]. In 1977, studies with the human bladder showed that *beta* adrenergic receptors in the bladder were neither *B*₁ nor *B*₂ subtypes [2], but it was not until 1999 when *B*₃ adrenoreceptors were identified as having a functional role in contributing to relaxation of the human detrusor muscle [2].

Mirabegron, a once daily, active *B*₃ adrenoreceptor agonist, is marketed for human use in the treatment of OAB and currently supplied in an oral controlled absorption system

(OCAS) tablet [5]. This allows for a sustained release of drug over a 24-h period. Mirabegron activates *B*₃ adrenoreceptors on the detrusor muscle in the urinary bladder, which in turn relaxes the detrusor muscle and increases bladder filling and storage [6]. In the past, antimuscarinics such as tolterodine, oxybutynin, and solifenacin were the mainstay for pharmaceutical treatment of OAB in humans. However, the use of these often resulted in numerous side effects including dry-mouth, blurred vision, and occasional urine retention [4]. Scientific studies were undertaken over the last decade to find a drug with comparable or superior therapeutic effects while minimizing negative side effects for humans [2, 8]. Study results proved mirabegron to be an excellent alternative to current mainstay therapeutics for OAB. Activation of *B*₃ adrenoreceptors in humans causes no adverse effects on bladder contraction and voiding, therefore, eliminating the risk of urine retention present with antimuscarinic drugs [4].

Mirabegron reportedly has an overall wide margin of safety in humans but less so in dogs. The most significant adverse effects in humans are an increase in mean pulse rate and change in baseline blood pressure as compared to antimuscarinic drugs [4]. Mirabegron increases the HR in healthy humans [7]; however, these changes are not believed to contribute to a risk of increased cardiovascular adverse events [4]. Dogs, however, show a more significant increase in HR than humans, likely due to a higher cross-activation of *B*₁ adrenoreceptors in animals as compared to humans [9]. A significant concern with the use of *B* adrenergic receptor agonists in general is the

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induction of positive inotropic and chronotropic output of the cardiac muscle predominantly due to B_1 adrenoreceptor stimulation [2]. This potentially leads to an increase in HR and BP. However, in vitro studies showed mirabegron to have minimal to no effects on B_1 and B_2 activity in humans and animals [2]. Due to the high selectivity of mirabegron to B_3 adrenoreceptors, serious cardiovascular effects are not anticipated. While this is true in humans, dog models used during initial preclinical studies showed serious and often fatal events that were not expected from these in vitro results. We sought to determine the effects and outcomes of mirabegron toxicosis in dogs.

Methods

Pet Poison Helpline (PPH), an international animal poison control center, maintains a database of all calls received regarding known or suspected exposures. A retrospective chart review of all calls within this database was performed for known or suspected mirabegron exposures between November 1, 2013 and December 31, 2015. Follow-up calls were performed and an attempt made to obtain medical records for each dog. The obtained medical records were reviewed by a single investigator. Information obtained included signalment, ingested mirabegron dose, concurrent exposures, treatments performed, effects observed, duration of effects, and post treatment follow-up. The dogs were categorized into one of four groups: exposures with medication found or retrieved after emesis, lost to follow-up but asymptomatic at time of consultation, dogs that remained asymptomatic, and those that became symptomatic. No dogs were excluded from the study due to concurrent ingestions and signs related to the concurrent ingestion were more expected to have been a result of mirabegron.

Results

The first call regarding mirabegron ingestion in a dog received by PPH was on November 19, 2013. From this initial call through December 31, 2015, the PPH received 23 calls involving 25 dogs with suspected mirabegron ingestions. The suspected ingested doses ranged from 1.31 to 8.9 mg/kg. Of the 25 eligible dogs for this study, missing medication was later found at home for 4 dogs and ingested medication was retrieved intact for 1 dog after inducing emesis, thus excluding 5 dogs and leaving 20 dogs in the study. For the purpose of this analysis, those remaining dogs were divided into those lost to follow-up but were asymptomatic at time of initial consultation (5 dogs), those that remained asymptomatic (9 dogs), and those that became symptomatic (6 dogs). No data are provided for the 5 dogs lost to follow-up leaving 15 dogs in the study.

Of the cases in the asymptomatic category, only two had a specific known ingested amount (Table 1). Both dogs had

emesis induced by their veterinarian followed by a single dose of activated charcoal (AC) orally (PO). Of these dogs, one with an ingested dose of 3.15 mg/kg, had no additional therapy performed after the initial emesis and AC. The second dog with an ingested dose of 5.5 mg/kg received intravenous (IV) fluids, a complete blood count (CBC), serum chemistries, and a repeat dose of AC 8 h after the initial dose. Serum chemistry results were within normal reference ranges and CBC results were normal with the exception of a mild leukopenia 3.38×10^9 K/uL (5.05–16.7 K/uL) which was believed to be an incidental finding. The remaining seven dogs had estimated ingested doses with a range from 1.5 to 8.9 mg/kg. These estimations were due to the owner's uncertainty about the actual number of mirabegron tablets ingested as well as two instances of more than one dog possibly ingesting the missing medication.

Six of the dogs developed clinical signs believed to be associated with mirabegron ingestion (Table 2). One dog developed erythema and periocular edema along with a transient mild elevation to hepatic enzymes. Of the remaining five dogs, two developed erythema and tachycardia, one developed erythema, tachycardia and panting, one developed tachycardia and vomiting, and one developed vomiting and hypertension.

Due to the limited veterinary information, each dog is presented as an individual case with summaries provided in Table 2.

Dog 1, a healthy 12-month-old, 18.3 kg, spayed female Labrador retriever mix, ingested an estimated dose of 5.46 mg/kg mirabegron three to 6 h prior to veterinary evaluation. Erythema to the perianal area and caudal abdomen was the only abnormality on examination. Emesis was induced with a single apomorphine tablet, unknown strength, placed in the conjunctival sac. Emesis was productive, but there was no evidence of medication in the vomitus. Ondansetron 0.15 mg/kg IV was administered and AC 1.3 g/kg PO given after emesis was complete. Initial chemistry showed mild elevations in serum alanine transferase (ALT) 78 U/L (8–75 U/L) and gamma-glutamyl transferase (GGT) 8 U/L (0–2 U/L). Erythema resolved within 4–8 h after ingestion. Heart rate and BP were monitored every 3–4 h and remained within the normal reference range throughout the dog's hospitalization. Approximately 12 h after mirabegron ingestion, the dog developed periocular edema which was treated and resolved with unknown doses of generic diphenhydramine intramuscular (IM) and dexamethasone SP IM. Serum alanine transferase was re-evaluated 24 h after ingestion using an individual chemistry test strip and the concentration was within the normal reference range at 38 U/L (10–225 U/L). Given the normal ALT results, reevaluation of GGT was not pursued.

Dog 2, a healthy 3-year-old, 10 kg, neutered male Jack Russell terrier, ingested 1.5 50 mg mirabegron tablets (7.2 mg/kg) within 2 h prior to veterinary evaluation. At presentation, the dog had severe erythema to the ventral thorax,

Table 1 Asymptomatic dogs after suspected mirabegron ingestion

Breed	Age	Weight (kg)	Ingestion suspected or known	Ingested dose (mg/kg)	Time from ingestion to onset of therapy (h)	Therapy performed
Jack Russell terrier	5 years	6.35	Known	3.15	1	AC HR monitoring
Miniature dachshund	5 years	4.5	Known	5.5	1.5	Emesis Anti-emetic AC and repeated at 8 h IV fluids CBC Serum chemistry HR/BP monitoring
Rat terrier	2 years	8.16	Known	1.5*	N/A	None
Yorkshire terrier	11 months	1.59	Known	1.97*	N/A	Emesis AC SQ or IV fluids
Bichon frise	6 years	10.9	Known	2.3–4.6*	3	Emesis Anti-emetic AC + cathartic IV fluids HR/BP monitoring Hepatoprotectant
Chihuahua	11 months	5.8	Suspected	8.6*	2.5	Emesis Anti-emetic AC + cathartic IV fluids Serum chemistry HR/BP monitoring Hepatoprotectants
Chihuahua	11 months	5.6	Suspected	8.9*	2.5	Emesis Anti-emetic AC + cathartic IV fluids Serum chemistry HR/BP monitoring Hepatoprotectants
Miniature Australian shepherd	7 months	9.8	Suspected	7.87*	1	Emesis Anti-emetic AC IV fluids Serum chemistry HR/BP monitoring
Miniature Australian shepherd	2 years	12.7	Suspected	5.9*	1	Emesis Anti-emetic AC IV fluids Serum chemistry HR/BP monitoring

*Estimated ingestion

abdomen, and perineal region. The heart rate was within a normal range of 136 bpm at presentation and the systolic blood pressure was 110 mmHg. Emesis was induced with apomorphine 0.03 mg/kg IV with one mirabegron tablet produced in vomitus. Dolasetron 0.6 mg/kg IV, AC with sorbitol 1.1 g/kg PO and IV fluids were given. Heart rate and BP were monitored hourly for 4 h and then decreased to every 2 h for 24 h due to animal's aggressive nature.

Tachycardia developed approximately 6 h after ingestion and remained elevated for 4 h before returning to normal. No therapy was given to treat the tachycardia. Blood pressure remained normal. Liver values were evaluated 24 h after presentation and remained within the normal reference range. S-adenosyl methionine (SAM-e) was initiated at the attending veterinarian's discretion at 31.25 mg/kg PO once daily for 10 days and dog was discharged.

Table 2 Symptomatic patients after suspected mirabegron ingestion

Breed/Age	Weight (kg)	Ingested dose (mg/kg)	Onset of signs (h)	Clinical signs	Treatment	Time to complete resolution of signs (approximate)(h)
Labrador retriever mix 1 year	18.3	5.46	6	Erythema Periocular edema Transient ALT/GGT elevation	Emetic Anti-emetic AC Serum chemistry HR/BP monitoring Diphenhydramine IM Dexamethasone SP IM	24
Jack Russell mix 3 years	10	7.19	2- erythema 6- tachycardia	Erythema Tachycardia	Emetic Anti-emetic AC Cathartic IV fluids Serum chemistry Hepatoprotectant HR/BP monitoring	10
German short haired pointer 11 weeks	5.27	3.4	2	Erythema Tachycardia	Anti-emetic AC Cathartic IV fluids Serum chemistry HR/BP monitoring	12
Bull terrier 3 years	24.65	2.03	2	Tachycardia Erythema Panting	N/A	N/A
Bichon frise 17 weeks	2.7	8.3	2	Tachycardia Emesis	Anti-emetic Butorphanol IV fluids Serum Chemistry Serum electrolytes HR/BP monitoring	> 17
Pug mix 12 years	9.53	1.31	1	Emesis Hypertension	AC IV fluids HR/BP monitoring	N/A

Dog 3, a healthy 11-week-old, 5.27 kg, intact male German short-haired pointer, ingested an estimated dose of 3.4 mg/kg mirabegron along with 0.09 mg/kg pramipexole one to 2 h prior to seeking veterinary care. The dog developed severe generalized erythema and an increased heart rate of 180 bpm within one to 2 h of ingestion. Pramipexole is a dopamine-2 agonist which anecdotally may produce tachycardia, ataxia, and tremors in doses exceeding 0.01 mg/kg. Erythema is not associated with pramipexole ingestions and was expected to be due to the mirabegron ingestion. Maropitant 2 mg/kg SQ, AC with sorbitol 250 ml PO (unknown concentration) and IVF were initiated and a serum liver profile performed. Laboratory values were within the normal reference range. Heart rate and BP parameters were monitored every 2 to 4 h for 24 h and remained within a normal range after the elevated HR on presentation. Erythema had resolved by the following morning and patient was discharged.

Dog 4, a healthy 3-year-old, 24.65 kg, spayed female bull terrier, ingested a known 2.03 mg/kg mirabegron dose 2 h prior to veterinary evaluation. This dog presented with tachycardia (heart rate not recorded but elevated according to attending veterinarian), diffuse erythema, and panting. Recommended treatment consisted of AC, IV fluids, beta blocker for persistent tachycardia defined as a HR greater than 180 bpm and sedation to aide in resolving tachycardia. The patient's owner declined to release veterinary records therefore treatment and outcome are unknown.

Dog 5, a healthy 17-week-old, 2.7 kg, intact female bichon frise, ingested 8.3 mg/kg mirabegron 2 h prior to veterinary evaluation. The dog presented with a heart rate of 220 bpm and systolic BP of 100 mmHg. Spontaneous emesis occurred while the dog was transported to the veterinary clinic but no evidence of medication was seen. Maropitant 1 mg/kg SQ, IVF, and butorphanol 0.19 mg/kg IV were given. Serum blood

chemistry and electrolytes were evaluated and results were within the normal reference range. Three and one-half hours after ingestion the heart rate increased to 280 bpm and remained elevated for approximately 13 h until declining to 200 bpm which was still considered tachycardia but significantly improved. No therapy was initiated for the tachycardia. The patient was discharged 17 h after ingestion with continued tachycardia that was believed by the practicing veterinarian to be due to excitement.

Dog 6, a healthy 12-year-old, 9.53 kg, spayed female pug mix, ingested a known 1.31 mg/kg mirabegron dose within 1 h of veterinary evaluation. Spontaneous emesis occurred in the examination room but the dog was otherwise asymptomatic on presentation. No medication was evident in vomitus. Activated charcoal 0.8 g/kg PO was given and IVF initiated. Heart rate and BP were monitored approximately every 2 h for 12 h. While HR remained within a normal range, systolic BP increased from 196 mmHg to as high as 227 mmHg with diastolic BP ranging from 69 to 139 mmHg and a mean arterial pressure (MAP) ranging from 129 to 179 mmHg (systolic 110–160 mmHg/diastolic 60–90 mmHg, MAP 85–120 mmHg). Comments from the attending veterinarian included a note that the blood pressures were within an acceptable range for this dog and no therapy was initiated. A corresponding decrease in HR occurred as the BP increased but this was always within the normal range for the patient's size and age. The dog was discharged 12 h post ingestion with no further follow-up. Bloodwork was not evaluated.

Discussion

Species variation occurs with each of the three specific types of beta receptors (B_1 , B_2 , and B_3). Frequency of B_1 agonist stimulation occurs with increasing occurrence in humans, dogs, rats, and monkeys, respectively [10]. $Beta_1$ adrenergic receptors, once activated, predominantly result in cardiovascular stimulation and cause an increased HR, increased contractility, and increased conduction velocity [1]. Frequency of B_2 agonist stimulation occurs with increasing occurrence in monkeys, humans, rats, and dogs, respectively [10]. Stimulation of B_2 adrenergic receptors results in a greater effect on smooth muscle intermediary metabolism by causing vasodilation, bronchial relaxation, lipolysis, glycogenolysis, and increased insulin secretion [1]. $Beta_3$ agonist stimulation, including effects from mirabegron, predominantly activates B_3 receptors in humans, rats, monkeys, and dogs [10]. In addition to relaxation of the urinary bladder detrusor muscle in humans, when activated, B_3 adrenergic receptors inhibit contractility in the ileum and colon, stimulate respiratory smooth muscle relaxation, produce peripheral vasodilation particularly of the skin and adipose tissue, stimulate certain calcium currents in the atrial myocytes, and reduce contractile force

of the ventricle [11]. Similar to B_1 and B_2 receptor agonists, mirabegron's effects in different species play a key role in clinical effects seen between humans and dogs after drug administration.

Absorption and distribution characteristics of mirabegron vary among many different species. Mirabegron is rapidly absorbed after oral administration in both humans and dogs [6, 10]. Oral availability is decreased and the absorption rate is prolonged in the presence of food where C_{max} and AUC are decreased 21.5 and 34.2%, respectively [5, 12]. Human oral bioavailability has a narrower range and overall lower bioavailability at 24–53% with fluctuations between males and females [5, 8]. In contrast, bioavailability in dogs ranges from 41.8, 64.6, and 77.1% at doses of 0.25, 0.5, and 1 mg/kg, respectively [6, 10]. At least 55% of mirabegron is absorbed in the GIT of humans, but this has not yet been established in dogs. A double peak effect occurs in humans with peak plasma concentrations at 0.5 to 1 h and again at 2 to 4 h post oral administration [6, 10]. It is believed that several factors contribute to varied absorption in humans including fractionated gastric emptying and staggered absorption areas along the intestinal tract [6]. In humans, plasma concentrations reached maximum concentration (C_{max}) between 2.7 and 5 h (h) which takes into account the double peak phenomenon [8]. The overall C_{max} is reached between 0.1–4 h after administration in dogs with clinical effects seen in as little as 30 min [6]. Again, the occurrence of double peak effect in dogs is uncertain. Enterohepatic recirculation, shown to occur in rats [12], is not believed to occur in humans based on a lack of fluctuating changes in plasma mirabegron concentration-time profiles after intravenous administration [6]. In humans, plasma protein binding is 71% but only 61–62% in dogs [12]. Mirabegron is widely distributed throughout all body tissues except the brain in humans [8, 9]. While not reported in humans or dogs, mirabegron is highly lipophilic [4] and passes through the placenta and milk in lactating rats [10] with deaths occurring several days after birth. Data suggests that a dose of 3 mg/kg in monkeys corresponds to a 50 mg maximum recommended human dose (MRHD) which is how a 3 mg/kg administration dose was established in dogs [13].

Mirabegron undergoes significant hepatic metabolism in humans [4, 8]. Eighteen metabolites have been identified in humans and other species [10], but studies have not been performed to identify these in dogs. At least 10 inactive metabolites are produced with none suspected of contributing to the drug's efficacy [2, 8]. Mirabegron is metabolized by several pathways including amide hydrolysis (48%), dealkylation, oxidative metabolism mediated by cytochrome P450, and glucuronidation and [2, 14]. One human study showed that circulating mirabegron metabolites represented a larger

percentage over parent compound when given orally versus intravenous (IV) administration suggesting that mirabegron undergoes intestinal and/or hepatic first-pass metabolism following oral administration [15]. The plasma half-life in humans is approximately 50 h [2] as opposed to a range of four to 10 h in dogs [12].

Elimination also varies with the species. Primary elimination of mirabegron in humans is in urine at 55%, with 45% unchanged, and feces at 34.2% [16]. The terminal elimination half-life in humans ranges from 26 to 65 h [8]. Varied doses along with oral and IV administration in humans resulted in similar elimination times resulting in the belief that elimination is not dose or route of administration dependent [15]. Elimination routes in dogs are currently unknown, but would be helpful in understanding the discrepancy between preclinical studies and actual cases.

The toxic dose of mirabegron has not been established in humans or dogs. An article reviewing six study publications in humans receiving mirabegron doses as high as 200 mg showed no toxicity and few adverse events [17]. The lethal dose has not yet been established in humans. While fatalities have been seen with doses > 3 mg/kg in preclinical studies of dogs, this has not been reproduced, therefore, an accurate LD50 is not yet established in dogs. Effects of toxicosis in dogs, however, have been reported at doses as low as 0.3 mg/kg in preclinical studies and include skin erythema, hypotension, tachycardia and disruption or destruction of the zygomatic salivary gland [10, 12]. As ingested doses increased up to 10 mg/kg, hepatotoxicity, ECG abnormalities including increased PR or QRS intervals, ventricular tachycardia with fibrillation and death occurred [10, 12]. Repeated dose preclinical studies of 2 weeks duration in dogs and rats confirmed suspected salivary gland effects including increased salivation, lacrimation, and atrophy of salivary glands [2, 10]. Dogs were found to be the most significantly affected with hemorrhage, atrophy, and necrosis of the salivary gland acinar and ductal cells after high exposures to mirabegron [2]. This was partially to fully reversible with cessation of drug [10, 12]. *Beta*₁ adrenoreceptor agonists are activated in the salivary secretory cells by sympathetic nerve stimulation or catecholamines, which cause the drooling behavior in carnivores as they prepare to attack [1]. Due to the potential for cross-activation of *B*₁ adrenoreceptors in dogs, this relationship likely explains why canine salivary glands appear to be more sensitive to mirabegron exposure than other species. There have been no clinical reports of decreased salivation or oral pain associated with salivary gland atrophy and there have been no reports of death in post-clinical data, pathology of salivation glands has not been performed. Hepatotoxicity and cardiovascular toxicity occurred in dogs enrolled in a high-dose study (exact dose unreported by authors) [2]. Hepatotoxicity was also reported during a 2-week repeated dose preclinical study as well as large acute ingestions [10,

12]. Hepatic indices including serum alkaline phosphatase (ALP) and ALT were transiently elevated less than twofold that of normal ranges [10]. Histopathology changes were only seen at or near the lethal dose of 20 mg/kg and with multiple exposures [10]. Histopathology changes included enlarged and yellow discoloration with mild to moderate hypertrophy, hepatocyte vacuolation, slight glycogen accumulation, and mild lipid deposits occurred at 25× MRHD [10, 12]. In surviving animals, all hepatic changes were reversible [10]. One dog in this retrospective study initially had very mild serum hepatic enzyme elevations, which returned to normal within 24 h. This was not considered to be related to mirabegron ingestion as the ingested dose was 5.46 mg/kg and the only additional related signs were erythema and periocular edema. It is possible that the result was due to laboratory error or variation in analyzer test strips used. Central nervous system (CNS) effects, including headaches reported in humans, are variable among species and have not been seen in dogs including the animals in this retrospective study.

During preclinical studies, cardiovascular toxicity occurred in dogs within all dosing ranges studied (0.3–10 mg/kg) and included ECG abnormalities, ventricular tachycardia, ventricular fibrillation, and death [10]. Tachycardia has been found to be the most common and significant effect of mirabegron toxicity in dogs. Elevated HR occurred at IV doses of 0.1 times the MRHD, 0.3 mg/kg, in dogs [10]. After oral dosing, mild elevations to HR and mild decreases to BP occurred in dogs [10, 12]. Higher doses resulted in ventricular tachycardia in dogs [10]. In dogs, a single oral dose of 0.3 mg/kg PO reduced systolic and mean BP by 30 and 10%, respectively, with no change to diastolic pressure [10]. An increase in HR occurred by approximately 100% at 3 mg/kg PO which persisted for 2 h and for 8 h at 10 mg/kg PO [10]. This is believed to be a response to the decreased BP [10]. Several mechanisms have been proposed to explain the increase in HR. One theory is that a compensatory vasodilating effect of *B*₃ adrenoreceptor stimulation occurs [2]. Other studies suggest that elevated HR at high doses is due to a direct chronotropic effect of off-target *B*₁ adrenoreceptor activation [2]. A preclinical study conducted in dogs to investigate the potential cause of tachycardia after mirabegron administration revealed that tachycardia is likely a reflex of the lowered BP at low doses [10]. This was also documented in another study where dogs were shown to have mild elevations in HR along with decreased BP [2]. However, at high doses of mirabegron, tachycardia may be due to direct activation of *B*₁ adrenoreceptors at cardiac myocytes and not strictly a compensatory mechanism of decreased BP [10]. Further studies to confirm this have not been performed. Mirabegron induced tachycardia in dogs was partially reversed with treatment of metoprolol, a *B*₁ adrenoreceptor antagonist [10]. This finding showed a causal relationship of mirabegron induced tachycardia and stimulation of *B*₁ adrenoreceptor agonists. Studies in humans reported cardiovascular-related events including

hypertension, QT prolongation, cardiac arrhythmia, and cardiac failure [9, 18]. It is possible that underlying cardiac disease was present as patients with significant cardiovascular disease were not excluded from any of these studies [9].

Discrepancies in cardiovascular effects in dogs have been seen in several separate studies and while acknowledged in the literature, the exact etiology remains unclear [5]. One study reported that the PR interval shortened after oral dosing in dogs at clinical doses [10]. No effect on QT_c was observed in dogs [10]. Cardiac histopathology was not evaluated. A second oral dosing study in dogs showed decreased BP and increased HR at doses greater than or equal to 10 mg/kg PO with no fatalities reported [10]. In this study, ventricular tachycardia was not observed with doses up to 100 mg/kg PO [10]. In contrast, a third study showed that at 0.3 mg/kg IV, the monophasic ventricular action potential duration was shortened and at 3 mg/kg IV, the HR was elevated, T wave heightened and QT prolonged [10]. Death from ventricular tachycardia (within 5–10 min) progressing to ventricular fibrillation (15 min) occurred in dogs given 10 mg/kg IV [10]. Yet another repeated dose study using 0, 1, 3, 10, and 20 mg/kg PO reported only one mortality believed to be mirabegron related at day three of a 20 mg/kg PO dosing regimen [10]. Pathology revealed subendocardial hemorrhage, white or pale spots to the in the ventricular wall and excess pericardial fluid [10]. This same dog developed ventricular tachycardia on the first day of 20 mg/kg PO dosing [10]. Additional study results revealed ventricular tachycardia at 20 mg/kg PO 2 h after dosing [10]. Based on this, all other dogs in this dosing group were euthanized for gross necropsy and histopathology [10]. In the same study, elevated HR occurred in the 1 and 3 mg/kg PO group but not statistically different than controls [10]. On the first day of dosing, PR interval increased within 2 h at 10 mg/kg and QRS slightly increased at 2 h with 10 mg/kg PO [10]. T wave amplitude elevated at 20 mg/kg. Effects on this at lower doses are not clear [10]. Finally, a study was performed using female beagles administered doses of 0–20 mg/kg PO for 3 days. All animals survived the study, but were euthanized for gross necropsy and histopathology. Use of dogs as a model species for additional preclinical studies was not pursued due to ECG and salivary gland findings [10]. It is interesting to compare the relative lack of cardiovascular findings in this retrospective study with the more serious ones present in preclinical and clinical studies. Tachycardia was the predominant cardiovascular sign and while hypertension occurred in one dog, the treating veterinarian felt it was within acceptable range for the patient.

In contrast, many of the less significant effects reported in canine preclinical trials (facial edema, hyperemia [described as erythema], ocular discharge, and emesis) [10] were present in dogs in this retrospective study. The etiology is unknown. One dog in a preclinical trial receiving 3 mg/kg PO developed facial edema involving the eyelids, periocular region, and muzzle and was reluctant to open the mouth [10]. The dog was euthanized

and the effects thought to be related to mirabegron exposure [10]. Hyperemia, seen at 1 mg/kg PO in another dog, was thought to be due to vasodilation and increased blood flow secondary to increased heart rate [10]. Erythema which resolved 1 week after cessation of mirabegron was noted in all dosing groups (ranging from 0.3–10 mg/kg) of yet another preclinical canine study [10]. Similar to these preclinical trials, hyperemia was the most common effect noted in this retrospective study with four of six symptomatic dogs exhibiting this sign. Emesis occurred at doses as low as 3 mg/kg PO in preclinical trials [10], but only one of the six symptomatic dogs treated during our retrospective study developed spontaneous emesis. Finally, in clinical trials ocular discharge occurred at 3 mg/kg and periocular and eyelid edema at doses as low as 1 mg/kg PO [10]. Only periocular edema was noted in a retrospective study dog with an ingested dose of 5.46 mg/kg.

Treatment recommendations for dogs ingesting mirabegron are formulated by the staff of Pet Poison Helpline based on information obtained from studies and case reports regarding the known and suspected pharmacokinetics and pharmacodynamics of the drug and are modified as additional canine specific information becomes available. Emesis followed by a single dose of activated charcoal is suggested for dogs presenting within 2 h of ingestion. A second dose of activated charcoal may be recommended in large ingestions due to questionable enterohepatic recirculation and OCAS delivery of medication. Intravenous fluids are recommended for cardiovascular support, in particular hypotension, with cardiovascular monitoring for 8 to 10 h based on the reported double peak in plasma concentrations in humans. Vasopressors should be considered if blood pressure is unresponsive to IV fluid therapy. Depending on the severity, tachycardia may be monitored closely or treated with β_2 adrenoreceptor antagonists or mild sedation with opioids. While only one symptomatic dog was treated with sedation for tachycardia, it is the opinion of the authors that all dogs with tachycardia due to mirabegron ingestion be monitored closely or treated to avoid any potential negative sequelae to prolonged tachycardia. Due to the inconsistent reported serum hepatic enzyme elevations in clinical trials, a hepatoprotectant such as SAM-e should be considered with ingested doses greater than 10 mg/kg. No treatment is recommended for erythema which appears to resolve spontaneously.

While it appears that oral ingestion in the nonclinical field environment does not lead to the significant life-threatening signs observed during preclinical trials, additional cases need to be evaluated to obtain a more accurate toxicity range in dogs. It is possible that the slow release nature of OCAS tablets minimizes the likelihood of toxicosis with the full concentration of the drug being released over a prolonged period of time rather than an acute, sudden release. In addition, it is reasonable to believe that toxicosis may be prolonged due to an extended period of drug release over a 24-hour timeframe due to this. Other factors such as individual animal variation and decontamination methods

may play an important role in the development of toxicosis. It is the authors' opinion, based on the combined results of several preclinical trials and inadvertent ingestions by dogs in the non-clinical field environment, that a more concerning level of fatal ingestions may be closer to 10 mg/kg; however, a larger sample number of dogs are needed to solidify the range of toxicity and mirabegron's effects on the animal. More specific recommendations regarding a toxic range can only be formed as data is collected from additional inadvertent ingestions.

The authors recognize certain limitations within this study. Several cases reported in this retrospective study are noted as suspected ingestions. A dog was suspected to have ingested the medication if a medication was dropped on the floor when the dog was in the vicinity, pill vial chewed open, and possible medication missing or medication that was once set out and became missing. Without witnessed ingestions, it is necessary to report these cases as suspected. If an animal were to have developed consistent signs of toxicity, the ingestion becomes much more likely, however, still remains as suspected. The authors are also limited to the medical records and varying degree of documentation provided for each patient as the initial patient risk and case management recommendations for each animal were made not by the authors, but by staff members unassociated with this study. Complete data provided from each case was analyzed and compiled by a single, uninvolved investigator after the case had been managed and the animal recovered. As with many retrospective studies, the sample size is limited. In this instance, mirabegron is a medication with limited human use which significantly impacts the potential exposure to animals in the home.

Conclusion

In conclusion, the conflicting reported effects of mirabegron between preclinical and nonclinical field environments demand that caution be used when evaluating a dog suspected to have ingested mirabegron. The most common observed effects in this small study were tachycardia and erythema, followed by emesis. Timely decontamination and goal-directed cardiovascular support should be considered until additional studies are done.

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Compliance with Ethical Standards

Conflicts of Interest None.

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