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Review Article

Review of the cardiovascular toxicity of amitriptyline treatment for canine neuropathic pain

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Abstract

Nowadays, the lifespan of pets has been increased by improvements in veterinary practice but age-related disorders are also increasing. Several nervous system attenuations are well-known to be the result of aging and/or pathological lesions. In many cases, neuropathic pain (NP) can develop and cause a significant impact on the clinical outcome and quality of life. With the difficulty in identification of the specific cause of NP, most NP management is planned according to clinical manifestations and recommended trial therapy. The drug of choice for trial therapy seems to be amitriptyline, a tricyclic antidepressant with multiple effects on neurotransmitter receptors and ion channels. However, the pharmacological effects of amitriptyline depend on several pathophysiological factors, including the level of drug exposure, drug metabolism capacity, concurrent disease and cellular responsiveness. In addition to its therapeutic effects, amitriptyline also possesses several adverse effects, especially cardiovascular toxicity. However, the information on its toxicity in veterinary clinical practice is very limited. In this article, we review the use of amitriptyline in NP management and its cardiovascular attenuation using both human medicine and veterinary publications. The aim of this review is to highlight the importance of routine cardiovascular monitoring and to provide a list of parameters that are associated with amitriptyline cardiovascular toxicity.

Keywords: amitriptyline, canine, cardiovascular toxicity, neuropathic pain

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Introduction

Neuropathic pain (NP), a pain sensation due to a somatosensory abnormality, requires correction of both the primary cause and deviated nervous activity. However, evaluation of the nervous activity is not a simple procedure, especially at the primary level of a health care unit. Also, the NP pathological processes usually take time for development and progression. Therefore, most NP cases manifest as chronic pain and their treatment plans are mainly based upon trial treatment constructed from medical publications, including clinical studies, case reports and guidelines.

However, in veterinary practice, a comprehensive neurological examination can only be performed in a small fraction of the referral animal hospitals and control clinical studies are also very limited. Hence, veterinary NP management is largely based upon human medical knowledge. With the growing number of animal patients with NP, trial therapy plans using several neuromodulating medications and physical treatments have been increasing. Among those medications, amitriptyline, a classic member of the tricyclic antidepressants (TCAs), is usually prescribed as one of the first-line drugs in many somatosensory system disorders (Mathews, 2008; Grubb, 2010). Although it is an antidepressant, it affects and alters several central and peripheral nervous functions, as well as ion channel activities, that are involved in the NP pathophysiology (Song et al., 2000; de Leon-Casasola, 2007). Nevertheless, its versatile actions are also capable of producing several adverse effects, especially in patients at risk of increased pharmacological responsiveness and active drug retention. In human medicine and animal toxicity models, amitriptyline is known to have cardiovascular toxicity in terms of both electrical and mechanical functions but there is no clinical report on this topic in canine patient. Therefore, we aimed to review the rationale of using amitriptyline for NP management and the cardiovascular toxicity manifestation in both humans and dogs. We hope that all of this amitriptyline information may be of benefit for veterinary practice.

Neuropathic pain

The somatosensory system conveys neural information, including proprioception, and the sensations of touch, heat, pressure and pain from both internal and external stimuli. Therefore, it plays a major role in the body's perception and response to all stimuli. However, impairment and abnormal function at any path of the nervous system can lead to somatosensory system disorders, in which perception and response to the somatic stimuli are inappropriate. The symptoms of somatosensory impairment are related to body sensations and manifest as neuromuscular signs such as sensory deficits (Kessner et al., 2016) and NP (Moore, 2016).

According to the International Association for the Study of Pain, NP is "pain initiated or caused by a primary lesion or dysfunction of the nervous system". In other words, NP is an unpleasant sensory sensation induced by various pain stimuli from a lesion or disease of the somatosensory nerve ending. These pain sensations are commonly reported as squeezing, pressure, burning, electric shock-like and stabbing sensations (Truini et al., 2013). Also, NP is often exhibited as a chronic pain that can be classified as hyperesthesia (pain from subthreshold noxious stimulus), allodynia (pain from non-noxious stimulus), and dysaesthesia (intermittent spontaneous pain) (Woolf and Mannion, 1999; Cashmore et al., 2009). The etiology and the pathogenesis of NP has been extensively elaborated upon in several studies in both human and veterinary medicine (Mathews, 2008; Garcia-Larrea, 2014; Jiménez-Yedra et al., 2014; Moore, 2016).

In human medicine, NP is a frequent clinical sign in patients with peripheral and central nervous system diseases and causes significant distress (Truini et al., 2013). The incident rates of NP in human studies vary from 1-3% of patients in the acute pain service (Hayes et al., 2002) to approximately 12% of the patients with chronic pain sensation who seek medical consultation (Pérez et al., 2009). However, in another study using the Leeds Assessment of Neuropathic Symptoms and Signs questionnaire, NP was detected in 47% of all participants and the NP showed a significant impact on their sleep and daily life (Hans et al., 2007). As a result, NP has been studied and reported extensively, especially in patients with stroke, spinal cord disease, multiple sclerosis, peripheral neuropathy from diabetic mellitus and chemotherapy and chronic osteoarthritis (Ohtori et al., 2012). This has led to the establishment of several clinical practice guidelines for NP (Cruccu et al., 2004; Moulin et al., 2014; National Institute for Health and Care Excellence, 2017; Western Australian Therapeutic Advisory Group, 2017).

In veterinary practice, a study of pain prevalence and type at a veterinary teaching hospital indicated that approximately 8% of dogs and 7% of cats suffered from NP (Muir et al., 2004). Furthermore, in those animals with pain from all types, aging was associated with a higher rate of pain. In addition, NP was reported to emerge from various etiologies (e.g., entrapment, trauma, inflammation and degeneration of nervous tissue), problems (e.g., pelvic fracture, spinal cord injury, intervertebral disc herniation, discospondylitis, vertebral osteomyelitis, diabetic neuropathy, tumors of the nervous system, inflammatory bowel disease and pancreatitis), and surgical procedures (e.g., amputation and inguinal hernia repair) (Mathews, 2008). Among these, intervertebral disc disease (IVDD) is the most common cause of spinal disease in dogs (Rusbridge, 2015) and the pathogenesis related with spinal degeneration is progressive with aging (Adams and Dolan, 2012). Nowadays, with the higher number of pets and their longer life expectancy due to advanced medical management, the chronic pain cases that fit with the NP criteria have been increasing in veterinary clinics. However, only a few clinical NP cases, for instance, canine peripheral nerve lesion and discospondylitis, and feline postsurgical pain (O'Hagan, 2006; Cashmore et al., 2009; Grubb, 2010) have been published in the veterinary field. This under-recognition in veterinary studies might be due to the difficulties in the identification and evaluation of NP (Moore, 2016).

The NP diagnosis and severity grading in humans require an integration of the information on the history of nervous system injury, an absence of evidence of ongoing nervous system injury, type of pain (e.g., allodynia, hyperalgesia or dysesthesias) and, most importantly, self-reporting by the patients of their pain characteristics (burning, stabbing or electric shock-like). Unfortunately, pets cannot provide this most crucial part of NP diagnosis, the self-reporting of the pain sensation. Therefore, NP assessment in pets employs gathering of information from the history of the nervous system injury or diseases, history taking from the owners about animal behavior patterns and pain expressions, especially any chronic pain that could not be improved by conventional analgesics, such as nonsteroidal anti-inflammatory drugs and opioids, and any chronic pain that impaired the pet's quality of life, together with the findings obtained from a through clinical examination and specific sensory testing for allodynia and hyperalgesia by experienced veterinarians. Common behavioral patterns in dogs and cats with NP reported by the owners are repeated scratching, biting and chewing at the specific part of the body and spontaneous pain expression with gentle petting (Grubb, 2010; Mathews et al., 2014). With advanced diagnostic tools and improved veterinary neuromuscular and orthopedic examination protocols, such as using electrodiagnostic testing in feline diabetic neuropathy evaluation (Mizisin et al., 2002), NP detection and management are becoming more informative.

Management of Neuropathic pain

The management of NP aims to both treat the primary cause of the somatosensory system disorders (if applicable) and to alleviate NP with a specific treatment depending on the suspected mechanism. Hence, NP management, especially in the early state, is a multimodal approach that combines several methods and medications to achieve the maximum pain control. Later on, when the severity of the NP is reduced, NP management can be tapered down and fewer combinations of medications or, rarely, a single medication may be able to maintain the analgesic effect. In general, the types of NP management can be classified into pharmacological and non-pharmacological managements.

Typically, pharmacological management of NP in veterinary medicine applies knowledge from human clinical trials, meta-analysis studies and guidelines. Most of the publications recommend TCAs (e.g., amitriptyline, nortriptyline and imipramine), serotonin/noradrenaline reuptake inhibitors (e.g., duloxetine and venlafaxine) and alpha$_2$-delta subunit of voltage-gated calcium channel modulators (e.g., pregabalin and gabapentin) over other medications, including opioids (e.g., tramadol, buprenorphine, oxycodone, morphine and methadone) and topical medications (e.g., alpha$_2$-adrenergic agonist, amantadine and lidocaine) (de Leon-Casasola, 2007; Finnerup et al., 2015). On the other hand, in animals, there has been no controlled study for NP treatment. However, commonly recommended medications for chronic pain induced by NP in dogs are pregabalin, gabapentin, amitriptyline and amantadine, an N-methyl-D-aspartate (NMDA) receptor antagonist (KuKanich, 2013; Jiménez-Yedra et al., 2014; Mathews et al., 2014; Moore, 2016). The same medications are used in cats except for pregabalin where there is no pharmacokinetic study or clinical research in cats (Baltzer, 2010; KuKanich, 2013; Epstein et al., 2015; Clark et al., 2017). For non-pharmacological management, acupuncture is the most common modality in pets with chronic pain, while medical massage, thermal modification, nutritional supplementation and environmental modification can be used as adjunctive pain management (Mathews, 2008; Corti, 2014; Epstein et al., 2015; Moore, 2016).

In Thailand, a multimodal approach is usually recommended for NP management in animals. For instance, for dogs with spinal cord injury induced by either IVDD or motor vehicle accidents that showed no pain improvement with conventional analgesics, veterinarians may also prescribe gabapentin and/or amitriptyline with a course of acupuncture (if applicable) as a clinical trial for NP management. Although gabapentin is considered the first choice to try in dogs with NP, if the NP shows no improvement with 2-4 weeks of gabapentin treatment, amitriptyline may be added to the NP management. The reasons for choosing these two drugs are mostly because of their availability for veterinary use, low cost and fewer drug regulations, compared with other drugs. Moreover, several clinical trials of gabapentin have been done in dogs (Cashmore et al., 2009; Wagner et al., 2010; Crociolli et al., 2015). However, with the short half-life (approximately 3-4 hours) of gabapentin in dogs (Vollmer et al., 1986), the need for frequent use (every 8 hours) may limit the application and might be the cause of mixed outcomes in clinical trials that prescribe gabapentin only twice a day. Even though amitriptyline has no experimental studies or controlled clinical trials on its analgesic ability in dogs, it is recommended by several veterinary publications (Mathews, 2008; KuKanich, 2013; Moore, 2016). Furthermore, there has been a case report in two dogs with NP that showed clinical improvement with amitriptyline within the first week of treatment (Cashmore et al., 2009).

Amitriptyline

Amitriptyline, a classic member of the TCAs, possesses diverse neuromodulatory actions resulting in antidepressant and analgesic effects. Its antidepressant action is caused by the blocking of brain serotonin and noradrenaline re-uptake (Bendtsen et al., 1996) as well as the serotonin receptor function (Fuxe et al., 1977). Its analgesic effect results from numerous mechanisms, including reduction in the brain serotonin and noradrenaline reuptake at the presynaptic level, suppression of ion channel activities (e.g., tetrodotoxin-sensitive and tetrodotoxin-resistant sodium channels, and voltage-gated potassium and calcium channels) (Song et al., 2000; de Leon-Casasola, 2007), inhibition of the NMDA receptor function (Watanabe et al., 1993), and augmentation of the gamma-aminobutyric acid (GABA) receptor activity (Dharmshaktu et al., 2012). Another analgesic

mechanism of amitriptyline is related to its anti-inflammatory effects (Rafiee et al., 2017). Thus, amitriptyline and other TCAs are considered as the first-line medication for human patients with NP, especially in cases of stroke, spinal cord injury and multiple sclerosis (Dharmshaktu et al., 2012; Moulin et al., 2014; Deng et al., 2016). Likewise, amitriptyline has been suggested for treating canine and feline NP associated with several causes (Mathews, 2008; KuKanich, 2013; Moore, 2016). A trial course of amitriptyline prescription is also strongly suggested for pets suffering from NP induced by diabetic neuropathy, inflammatory bowel disease and feline interstitial cystitis (Mathews, 2008).

Pharmacokinetic studies of orally administered amitriptyline in dogs reveal that amitriptyline exhibits a peak plasma concentration at 0.5-2 hours after ingestion with a short half-life of 5-6 hours (Boeck and Jørgensen, 1980; Kukes et al., 2009; Norkus et al., 2015). Amitriptyline has a higher bioavailability in fasted dogs than that in fed dogs (91% and 69%, respectively) suggesting that food in the GI tract might affect the drug's absorption (Norkus et al., 2015). In the blood circulation, the lipophilic TCAs are bound to the plasma protein and distributed into most body tissues and maternal milk (Wismer, 2000; Plumb, 2018). The hepatic metabolism of the drug is very important for amitriptyline elimination as 95% of this drug is metabolized by hepatic cytochrome P450 oxidative enzymes (Thorn, 2017). In dogs, the level of nortriptyline, an active metabolite of amitriptyline that also produces pharmacological effects, showed a positive correlation with amitriptyline exposure (Norkus et al., 2015). Nortriptyline showed a longer half-life in humans, at approximately 16-38 hours (Verbree et al., 2016). This overlapped circulation of amitriptyline and nortriptyline could aggravate their pharmacological effects. Besides hepatic function, renal clearance plays a major role in inactive-metabolite elimination (Rudorfer and Potter, 1999). Therefore, hepatic and renal functions, as well as other medications that require the same groups of hepatic enzymes for their metabolism, heavily affect the plasma concentration of amitriptyline and its active metabolite. To prevent the side effects and toxicities of TCAs, proper titration is crucial. TCAs should be prescribed at a low dose once daily at bedtime and then the dosage can be increased every 3-7 days depending on the patient's tolerance to the therapeutic dose (Dharmshaktu et al., 2012).

Although, there have been no pharmacological analysis on the effectiveness of TCA treatment of NP in dogs and cats, the recommended oral dose of amitriptyline in dogs in recent veterinary pharmacology textbook is 3-4 mg/kg every 12 hours (Plumb, 2018). This dosage is extrapolated from the pharmacokinetic data in a canine study and other human clinical studies (Kukes et al., 2009), and is higher than the previously recommended dose of 1-2 mg/kg once or twice daily (Mathews, 2008; KuKanich, 2013). In cats, the recommended oral dose is 0.5-1 mg/kg or 2.5-12.5 mg per cat, once daily at night (Mathews, 2008; Baltzer, 2010; Plumb, 2018). However, amitriptyline is considered as an extra-label drug for both dogs and cats (Plumb, 2018). The onset of clinical improvement in pets varies from as fast as 48 hours to approximately 2-4 weeks after starting the medication (Mathews, 2008). In responsive cases, amitriptyline can gradually attenuate pain over time. For instance, a case report in three dogs with NP showed that two dogs responded well with amitriptyline at 1.1-1.3 mg/kg orally twice daily within the first week, whereas the third dog given amitriptyline at 1.4 mg/kg orally twice daily for two weeks, had the side effect of mental alteration without any pain improvement (Cashmore et al., 2009). For discontinuation, amitriptyline should be slowly tapered down (Boothe, 2011; Plumb, 2018).

Importantly, TCAs treatment is not always safe. In addition to their therapeutic effects, numerous side effects of amitriptyline have been reported and range from mild reactions to a lethal problem. Mild adverse effects include developing mental alteration, gastrointestinal upset, anticholinergic sign, alopecia and allergic skin reaction (Kerr et al., 2001). The serious cardiovascular problems associated with amitriptyline treatment in humans include myocardial infarction, stroke, arrhythmias, hypotension or hypertension and tachycardia, according to the U.S. Food and Drug Administration (FDA) prescribing information. All of these side effects can develop when administered within or above the therapeutic doses, although lethal reactions are more frequently found in overdose cases. In dogs, a TCA overdose can alter mentation, reduce gastrointestinal movement and cause several other clinical signs such as dyspnea, vocalizing, ataxia, seizure, hyperthermia, hypotension, arrhythmia and death (Wismer, 2000; Plumb, 2018). Information on the adverse effects of amitriptyline at therapeutic dosages in dogs is insufficient, where only mental alteration and vomiting have been mentioned (Cashmore et al., 2009; Norkus et al., 2015). However, in experimental amitriptyline intoxication studies, conscious dogs had clinical signs of sedation, vomiting, restlessness and seizure (Boeck and Jørgensen, 1980). Most importantly, these dogs developed cardiovascular toxicity that could lead to their death without proper treatment (Boeck and Jørgensen, 1980; Nattel et al., 1984; Sasyniuk et al., 1986; Yokota et al., 1987; Wismer, 2000).

Cardiovascular toxicity associated with amitriptyline

Cardiovascular toxicity is the most prominent side effect of TCAs found in both therapeutic regimens and overdose cases, as it significantly impacts the clinical outcome. Most importantly, this cardiovascular attenuation can cause hemodynamic disruption and death in severe cases. In fact, this side effect is the major cause of death in TCA toxicity (Williams and Sherter, 1971). The toxicity can develop in both patients with and without previous cardiovascular defects. However, the severity of these problems is dependent on the TCA plasma concentration and cardiovascular status (Glassman et al., 1988). In patients who experienced cardiovascular side effects, plasma concentrations of TCAs could be as low as 50 ng/ml, which is lower than the optimal concentration (150-300 ng/ml) for the therapeutic effect (Simpson et al., 1983). Thus, the use of TCAs has raised safety concerns over the past few decades (Yekehtaz et al., 2013). Several

physicians and medical associations have suggested that a more intensive monitoring should be mandatory in all patients, especially for geriatric, patients with underlying cardiovascular problems such as myocardial ischemia, conduction disturbance, ventricular arrhythmia and atrial fibrillation, as well as patients receiving a high dose of TCAs (Burrows et al., 1976; Burgess et al., 1979; Glassman et al., 1993; Kerr et al., 2001). As electrocardiogram (ECG) alterations in most of the cardiotoxicity cases associated with TCAs could be detected before the onset of clinical signs (Açikalin et al., 2010), ECG monitoring has become a more essential tool than monitoring the serum drug concentration for risk stratification of the toxicity of TCAs in medical practice (Verbree et al., 2016).

Likewise, association between TCAs and cardiovascular status has been found in animals. For instance, in dog studies, the administration of a high dose of amitriptyline has caused serious cardiovascular problems that were positively correlated with the amitriptyline plasma levels. Moreover, amitriptyline showed a more pronounced effect on infarcted myocardium than normal myocardium (Boeck and Jørgensen, 1980; Nishimoto et al., 1990). Interestingly, a single oral amitriptyline administration at approximately 8 mg/kg could produce a plasma concentration range from 22 to 127 ng/ml (Norkus et al., 2015), while chronic amitriptyline administration (0.7-3.3 mg/kg twice daily) for canine behavioral problems resulted in a serum concentration from less than 20 to 350 ng/ml (Reich et al., 2000). Therefore, canine patients receiving recommended amitriptyline dosage should be monitored for cardiovascular side effects as well. Cardiovascular monitoring, at least heart rate and rhythm, is also recommended during amitriptyline treatment in veterinary practice (Papich, 2011).

As mentioned above, amitriptyline as well as other TCAs have central and peripheral neuromodulatory and multi-ion channel blocking effects that can affect not only neuronal alteration but also cardiovascular function. In severe cases, the cardiovascular toxicity that results from TCAs can cause serious cardiac electrical alterations and cardiovascular mechanical disturbances.

Electrocardiogram alterations: Abnormal cardiac electrical properties induced by TCAs, especially during an overdose, are often present as sinus tachycardia, ventricular tachycardia, ventricular fibrillation, Torsade de pointes, bradyarrhythmia and conductive block (Abeyaratne et al., 2016). From all of the TCAs actions, catecholamine reabsorption inhibition at the presynaptic adrenergic nerve ending of the heart, as well as the anticholinergic and sodium channel blockade effects on cardiac tissue are well-known causes of cardiotoxicity. These TCAs effects alter cardiac electrical functions both the impulse generation and the conduction property leading to a wide variety of cardiac electrical disturbances and clinical hemodynamic manifestations.

In terms of cardiac impulse generation, TCAs can augment both enhanced automaticity and triggered activity. Accordingly, TCAs affect both pacemaker and ectopic foci leading to arrhythmia from various origins. Sinus tachycardia is the most common cardiovascular side effect in TCAs toxicity cases, while ventricular dysrhythmias (e.g., ventricular premature contraction (VPC), idioventricular rhythm, ventricular tachycardia and ventricular fibrillation), as well as other ECG abnormalities, including supraventricular tachycardia, bradycardia, sinus arrest and pulseless electrical activity are less prevalent (Thanacoody and Thomas, 2005). The combination of an anticholinergic effect and a hyper-adrenergic state induced by the inhibition of norepinephrine (NE) reuptake seems to be the primary cause of sinus tachycardia associated with amitriptyline in dogs, and this augmentation in the heart rate has been positively correlated with the dose or plasma concentration of amitriptyline (Boeck and Jørgensen, 1980; Ikeda et al., 1996). The hyper-adrenergic state is suspected to be a major mechanism for the increased sinus rate, as concomitant administration of propranolol, a beta-adrenergic blocker, can prevent the elevation of heart rate induced by amitriptyline in anesthetized post-myocardial infarction dogs (Ikeda et al., 1996). In humans, amitriptyline also has a tendency to increase the heart rate, especially in patients that have a lower heart rate before receiving medication (Glassman and Bigger, 1981). This augmentation in the heart rate could be a subclinical finding and the increased heart rate was approximately 16 beats per min in the chronic moderate dosage (Ziegler and Biggs, 1977).

For ventricular dysrhythmias, the ventricular tachyarrhythmia induced by amitriptyline in dogs could result from an increased triggered activity rather than an enhanced automaticity (Nattel, 1985). In a study on rabbits, the inhibition of presynaptic NE reuptake, which could enhance the myocardial catecholamine sensitivity, was found to play a major role in the ventricular dysrhythmia induced by TCAs, including amitriptyline (Barth et al., 1975). These ectopic impulse generation abnormalities can also originate from the infarcted area. As can be seen in the myocardial infarction dog model, amitriptyline increased the inducible ventricular arrhythmia events in these dogs (Nishimoto et al., 1990). In addition, the cardiac sodium and potassium channel blockades of TCAs, including amitriptyline and nortriptyline, can prolong the cardiac action potential duration and refractory period resulting in an increased risk of dysrhythmias from ectopic foci, and most importantly Torsade de pointes, a lethal polymorphic ventricular tachycardia associated with QT interval prolongation (Thanacoody and Thomas, 2005; Verbree et al., 2016). There are several other risk-amplifying factors of Torsade de pointes that should be considered, such as age-related drug clearance attenuations, high plasma drug concentrations, other confounding medications, electrolyte disturbances, mainly hypokalemia and hypomagnesemia, as well as coexisting cardiac problems (Wenzel-Seifert et al., 2011). Interestingly, the medication dosage was not considered to be a sensitive predictor for cardiotoxicity, especially in geriatrics whose plasma drug level relied greatly on other pharmacokinetic factors (Hefner et al., 2018). However, several researchers have suggested that TCAs induce an antiarrhythmic effect due to their inhibition of the inward sodium current, the same mechanism as class I

antiarrhythmic drugs, and some TCAs, including imipramine, were found to be safe for use in patients with ventricular ectopic beats (Glassman and Bigger, 1981; Glassman et al., 1993). Bradyarrhythmias have been reported rarely (Brackenridge et al., 1968; Lebre et al., 1995) and the slower heart rate was most likely to result from the delayed conduction effects, especially at the atrioventricular (AV) node (Thanacoody and Thomas, 2005).

Besides dysrhythmia, the conductive block is also a hallmark of the cardiac toxicity of TCAs, especially in overdose patients. Various degrees of cardiac electrical conduction alterations in both the myocardium and the cardiac conductive pathway can be induced by TCAs at the level of the AV nodal and the ventricular conductions. This conductive side effect, which mimics class I antiarrhythmics, is described as a "quinidine-like" effect that can slow the distal conduction system, such as His-Purkinje conduction, rather than AV nodal conduction. In patients using TCAs, a right bundle branch block (RBBB) pattern, as detected by ECG, and a reduced conduction velocity of the bundle of His, the bundle branches, and Purkinje fibers, as measured from His bundle electrocardiography, have been reported (Burrows et al., 1976). The prolongation of ventricular conduction in some cases can produce ECG alterations from a normal sinus wave form to a left bundle branch block (LBBB), RBBB and bilateral bundle branch block, as well as a complete heart block, especially in amitriptyline overdose cases (Brackenridge et al., 1968; Kramarz and Foryś, 2013; Yekehtaz et al., 2013; Li and Lamichhane, 2017). Another possible explanation for the attenuation of the cardiac distal conduction is myocardial damage, which has also been reported in cases of amitriptyline and nortriptyline overdose (Brackenridge et al., 1968). Moreover, in patients with a TCA overdose, prolongation of the QRS duration and corrected QT interval (QTc) are important risk stratifications for the prediction of complications (Verbree et al., 2016), especially for amitriptyline, where its serum level had a significant correlation with QTc prolongation (Hefner et al., 2018). On the other hand, prolongation of the PR interval or QRS duration were strong indications of a supra-TCA therapeutic window (Glassman and Bigger, 1981).

Likewise, amitriptyline can depress the canine Purkinje fiber depolarization rate (Vmax) via blockade of cardiac sodium channels (Nattel, 1985) and the dose-dependent conductive block associated with TCAs in animals. A single oral dose of amitriptyline at 70 mg/kg in dogs resulted in prolongation of the PR and QRS intervals that progressed to RBBB and LBBB within the first few hours after drug administration (Boeck and Jørgensen, 1980). Concordantly, intravenous injection of amitriptyline at 0.3-1 mg/kg in anesthetized dogs resulted in a marked prolongation of the PR and QRS intervals, as well as QTc. Moreover, the dogs developed ventricular fibrillation or cardiac arrest at a dose of 10 mg/kg (Yokota et al., 1987). Nishimoto and colleagues (1990) also found that intravenous injection of amitriptyline at 1 mg/kg significantly slowed the ventricular conduction in normal myocardium, and the ventricular conduction of infarcted myocardium was delayed at the higher dose. Amitriptyline also increased the dispersion of the ventricular refractoriness measured from the effective refractory period in post-myocardial infarction canine models but a combination administration with propanol could not alter this period (Ikeda et al., 1996). These findings indicated that direct cardiac suppression by the "quinidine-like" effect was the principal mechanism for some types of the ventricular arrhythmias, as the delay in the ventricular conduction and the prolongation of the refractory period can significantly increase the risk of ventricular reentry arrhythmia. Nevertheless, most of the mild to moderate amitriptyline cardiovascular effects were reversible within a few days in dogs (Boeck and Jørgensen, 1980; Xin and Liu, 1986).

Although there has been no clinical report on these conduction disturbances in canine patients receiving TCAs at a therapeutic dosage. A study in canines with behavioral problems that required chronic treatment of TCAs revealed that only one dog from a total of 39 dogs had RBBB that might be associated with medication (Reich et al., 2000). Last year, we also examined a dog with IVDD induced NP that was treated with oral amitriptyline at 0.3 mg/kg twice daily who exhibited RBBB (figure 1) and hypertension after 3 days of amitriptyline treatment. The cardiovascular disturbances in this dog were not seen before amitriptyline administration and the cardiac structure was unremarkable after amitriptyline administration, as evaluated by ECG and echocardiography. Hence, the potential association between RBBB and amitriptyline could not be ignored. Moreover, this geriatric dog also had an ongoing problem of multiple hepatic nodules (approximately 1.5-4.1 cm in diameter) with moderate to severe bile retention and increased liver enzymes that had been manifested for years. Therefore, this dog was at risk of TCA-induced cardiovascular toxicity even at a low dosage of amitriptyline, compared with other younger and healthier dogs.

Other ECG waveform alterations associated with TCAs have been reported in several cases, including a shortened QT interval, ST elevation or depression, as well as diphasic, inversed and alternated T waves (Bolognesi et al., 1997; Enslin and Nikolić, 2005; Abeyaratne et al., 2016; Lubna et al., 2018). In a study in an anesthetized dog model, amitriptyline at a plasma concentration of approximately 100-fold more than the therapeutic concentration caused a significantly lower QT interval and QTc than those values before the drug administration (Lubna et al., 2018), which is contrast to the typical long QT syndrome and a torsadogenic potential of amitriptyline described in other literature. Moreover, the inhibition of the inward sodium current and the ST elevation induced by amitriptyline in several cases fit with the criteria of Bruganda syndrome. Thus, the suggestion that amitriptyline might be able to produce Bruganda syndrome is of concern. Furthermore, the combination of arrhythmias and conduction disturbances can also develop, as their mechanisms and target cells do not always overlap. The ventricular conduction block occurs at the ventricular conductive tissue, while the ventricular ectopic beat may be associated with an increased

trigger activity of the ventricular myocardium. Therefore, prolongation of the QT interval or the bundle branch block pattern can present simultaneously with the ventricular ectopic beat or tachycardia in some cases (Brackenridge et al., 1968).

For cardiac electrical monitoring, a routine ECG monitoring is not the gold standard for arrhythmia detection. However, sustained abnormality in the heart rate and ECG patterns can easily be detected by routine ECG monitoring, and the VPC that could be detected from a 2-minute ECG recording showed a high correlation with high frequency VPC using 24-hour ECG recordings (Evenson et al., 2000). Thus, regular ECG monitoring is still strongly recommended in all patients receiving TCAs but more caution should be used when interpreting the QTc from cases that have a bundle branch block pattern, as this ECG pattern can reduce the accuracy of the QTc measurement. Lately, researchers have tried to evaluate the QT interval and QTc in patients with bundle branch block using a modified JT and JTc equation, that takes the QRS interval and uses a fixed adjustment value for each gender, rather than the normal measurement of the QT interval or QTc, to quantify the risk of serious arrhythmia, especially Torsade de pointes (Yankelson et al., 2018). Unfortunately, there has not been a study on the JT correction for the bundle branch block in dogs and QTc calculated from the ECG of dogs with RBBB or LBBB cannot be used directly to estimate the risk of developing serious arrthymias. Therefore, ECG screening before starting amitriptyline and regular ECG monitorings during the course of treatment should be planned in all cases, especially in patients with a preexisting cardiovascular problem (Glassman and Bigger, 1981). The cardiac electrical toxicity induced by TCAs in dogs requires further cardiac evaluation tools together with clinical manifestation to improve the risk-stratification and to determine the severity of the problem.

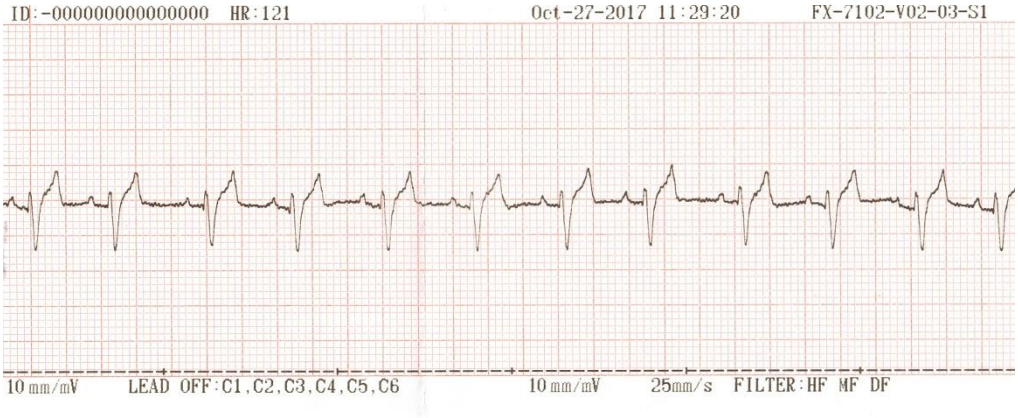

Figure 1 Lead II ECG trace obtained from a geriatric dog after 3 days of amitriptyline treatment showing the sinus rhythm with short R wave, deep and broad S wave, and slightly prolonged QRS complex referred to right bundle branch block (RBBB).

Cardiac mechanical attenuations: Myocardial depressions due to the toxicity of TCAs can be expressed as a conductive defect and mechanical dysfunction. Several mechanisms are involved in the direct negative inotropic effect, such as outward potassium current augmentation, as well as inward sodium and calcium current inhibition via multichannel blockade effects of TCAs (Casis and Sánchez-Chapula, 1998; Minoura et al., 2012). The reduction in myocardial contractility, evaluated from the maximal rate of rise of left ventricular pressure ($LVdP/dt_{max}$), has been shown in many animal models, including dogs, and amitriptyline affected the contraction in both healthy and infarcted myocardium (Nishimoto et al., 1990; Lubna et al., 2018). This cardiotoxicity was exhibited in a dose-dependent manner. At a therapeutic plasma level, amitriptyline did not alter either ECG or mechanical cardiac performance, while it increased the $LVdP/dt_{max}$ at a level of 10-fold higher than the therapeutic plasma level. The ventricular mechanical function was significantly depressed in the anesthetized dog model at a 100-fold higher level than the therapeutic plasma level (Lubna et al., 2018). However, in these dogs, the cardiac output relied more on the heart rate than the ventricular contraction suggesting that this contractility depression was not lethal. For clinical application, most of the animal studies used TCAs at very high doses and so the findings may more accurately relate to the overdose cases. Whereas, TCAs are administrated in therapeutic regimens, the myocardial dysfunction may not develop into clinical impairment in healthy subjects.

At a therapeutic dosage, the effect of amitriptyline on the left ventricular performance was inconclusive. Most of the early phase studies evaluated the patients' myocardial contractility using an indirect cardiac index from the seismocardiogram and ECG. The parameters from this method are the systolic time intervals (STI), e.g. left ventricular ejection time (LVET), the aortic pre-ejection period (PEP), PEP/LVET ratio, and the electromechanical systole (QS_2). The STI measurement details have been elaborated on thoroughly in the study by Reant and colleagues (2010). In healthy volunteers, amitriptyline could augment the ventricular contractility measured from seismocardiogram and ECG, or depress the ventricular systolic function depicted by the PEP prolongation (Kopera et al., 1980; Warrington et al., 1989). In clinical studies, amitriptyline produced some mild ventricular performance attenuations, as determined by the STI alterations, including the prolongation of the PEP, increased PEP index and PEP/LVET ratio, as well as by 2D-echocardiographic

ventricular performance attenuation, in terms of the reduction in the ejection fraction (Burgess et al., 1979; Galetta et al., 1993).

Besides subclinical contractile dysfunction, TCAs, especially amitriptyline and clomipramine, have raised concerns as drug-induced cardiomyopathies due to their cardiotoxicity and potential associations with clinical cardiovascular outcomes (Feenstra et al., 1999; Montastruc et al., 2010). The mild ventricular dysfunctions in those patients are more noticeable under cardiac stress, including the exercise stress test and cardiovascular comorbidity. In the case of a severe ventricular conductive block, dyssynergic ventricular septal motion can be found in the echocardiogram (Li and Lamichhane, 2017). Therefore, preexisting cardiovascular problems and other coincident factors can superimpose the amitriptyline outcome in terms of ventricular performance. Unlike humans, there is no available controlled clinical study in canine patients on the effects of amitriptyline on left ventricular performance.

Although the STI showed a high feasibility and correlation with the left ventricular ejection fraction in clinical practice, other important factors, such as left ventricular preload and afterload, as well as the cardiac electrical status significantly impact upon the STI values (Reant et al., 2010). With the various cardiac electrical effects of amitriptyline, including alterations in heart rate and ventricular conduction ability, the evaluation of the ventricular performance using STI should be done with more caution. Thus, more comprehensive cardiovascular evaluations should be performed in all at-risk patients.

Hemodynamic disturbances: Orthostatic hypotension is one of the most serious cardiovascular toxicity effects of TCAs, particularly in the elderly, as this postural hypotension can cause intense physical injuries such as hip fracture, open wounds and head concussion (Glassman and Bigger, 1981). Among the drugs in the TCA family, orthostatic hypotension is more common with imipramine than amitriptyline and nortriptyline. In a control study, the administration of amitriptyline at a therapeutic dosage for seven consecutive days produced a significant increase in the postural hypotension, as measured by the differences in both the systolic standing blood pressure and the diastolic recumbent blood pressure. However, none of these healthy participants exhibited signs of unconsciousness (Kopera, 1978). The exact mechanism of TCAs-induced orthostatic hypotension has not been clearly elucidated. However, links have been made between the postural hypotension and the increased peripheral vasodilatation due to alpha$_1$-adrenergic receptor blockade, the negative inotropic effect, as well as life-threatening arrthymias. These effects can also explain the systemic hypotension in the patients with TCA intoxication, in which systemic hypotension is a common hemodynamic alteration (Brackenridge et al., 1968; Kerr et al., 2001; Verbree et al., 2016). This hypotensive effect can be intensified by other concurrent problems, including dehydration, systolic dysfunction and other medications that suppress cardiovascular functions.

In contrast, TCA-mediated cardiovascular toxicity can also manifest as hypertension. This side effect has been presented in several clinical reports, such as in patients with panic disorders (Louie et al., 1992), depression (Hessov, 1971) and amitriptyline poisoning (Brackenridge et al., 1968). This hypertensive effect could result from autonomic imbalance at the cardiac level leading to increased cardiac output and by increased NE function at the alpha$_1$-adrenergic receptor of the vessel resulting in augmentation of vasoconstriction and total peripheral resistance (Licht et al., 2009).

In dogs, the hemodynamic alterations associated with TCAs are also inconclusive and the information is solely provided by acute toxicity studies. Oral administration of amitriptyline at toxic levels showed mixed results in terms of the blood pressure in laboratory dogs, where stable, markedly reduced or increased blood pressure were presented by different dogs in the same study setting (Boeck and Jørgensen, 1980). However, none of these dogs exhibited any serious hemodynamic disturbance that required treatment. On the other hand, in another dog study, the intravascular administration of amitriptyline at a high dose resulted in a marked reduction in systolic blood pressure followed by a slight increase towards baseline value (Yokota et al., 1987). Although, the average mean arterial blood pressure of each dog was within the physiological level, half of the dogs died from cardiac arrest and ventricular fibrillation. Moreover, administration of amitriptyline intravenously at doses to give a plasma drug concentration of 1-, 10- and 100-fold therapeutic doses to anesthetized dogs caused no alteration in their cardiovascular parameters at a low dose, and a temporary significant reduction in the total vascular resistance with an elevated heart rate, cardiac output and left ventricular contractility at a medium dose, without any significant change in the mean arterial blood pressure (Lubna et al., 2018). However, at a high dose, the mean arterial blood pressure was transiently decreased together with total vascular resistance, while the heart rate, cardiac output and left ventricular contractility were augmented. Nevertheless, no dog developed lethal cardiohemodynamic collapse. These results indicate that the cardiac function that determines the cardiac output was the controlling factor for the cardiohemodynamic outcome in these studies. Hence, blood pressure monitoring alone is neither sufficient for risk stratification nor severity evaluation of TCA toxicity.

Amitriptyline cardiovascular toxicity treatment: For all cases of TCA poisoning by acute ingestion, elimination of further gastrointestinal absorption is the first step that should be performed within the first hour of medication exposure. In dogs, inducing emesis should be performed only in the absence of clinical signs, as emesis can cause aspiration in animals with a low level of consciousness. Rather, repeated oral administration of activated charcoal together with a cathartic to reduce the gastrointestinal absorption of the TCAs and increase the drug elimination is recommended (Wismer, 2000). Since TCAs can suppress the gastrointestinal motility leading to

increased absorption time, a magnesium salt cathartic should not be used. In humans, gastric lavage is another treatment option for gastric decontamination but it has shown inconclusive results in reducing the gastrointestinal drug absorption (Kerr et al., 2001; Body et al., 2011). However, airway intubation with oxygenated air is highly recommended for all unconscious patients to prevent iatrogenic aspiration and further hypoxia.

For the initial clinical assessment at least a physical examination, ECG, blood pressure and blood gas monitoring should be used. Intravenous fluid therapy is recommended to treat TCA-induced hypotension. However, in hypotensive cases that are not responsive to fluid therapy, administration of adrenergic agonists can be used for positive inotrope and vasopressor effects. Epinephrine and NE have been found to be more effective in treatment of TCA-induced hypotension than dopamine, because the dopamine efficacy can be depressed by the fact that TCAs can cause NE depletion at the presynaptic nerve terminal (Kerr et al., 2001; Body et al., 2011).

In more complicated cases including patients with cardiovascular toxicity (i.e. QRS prolongation, dysrhythmias or hypotension) or acidosis, in which their blood gas can be closely monitored, intravenous administration of sodium bicarbonate is a standard therapy in humans (Body et al., 2011). For canine patients, administration of sodium bicarbonate at 2-3 mEq/kg is recommended as well (Wismer, 2000). Sodium bicarbonate treatment has shown several benefits in cases of TCA poisoning (Verbree et al., 2016). First of all, it can increase the sodium gradient across the sodium channels leading to alleviation of the negative effects of TCAs on the sodium channel function and action potential generation (Sasyniuk et al., 1986). In addition, sodium bicarbonate can buffer the acid, and so the plasma pH is maintained at a mild alkalosis range. The alkalosis serves two main purposes of (i) to facilitate the TCA dissociation from the cardiac sodium channel to reduce the arrhythmogenic effect and (ii) to increase the TCA binding ability to plasma proteins and decrease the availability of the pharmacologically active form. The preferred plasma pH in the treatment of TCA toxicity is 7.45-7.55 in humans and at least 7.50 in dogs (Nattel et al., 1984, Body et al., 2011). Therefore, the alkalinisation effect of sodium bicarbonate administration is more effective than only increasing plasma sodium level with saline fluid (Kan et al., 2014). In the amitriptyline intoxicated dog model, sodium bicarbonate could reverse the ventricular tachycardia to a normal sinus rhythm and attenuate the hypotensive effect of amitriptyline within the therapeutic duration that correlated with the plasma pH (Sasyniuk et al., 1986). However, the complications associated with the sodium bicarbonate induced severe acid-base disturbance are serious, including dysrhythmias.

Although cardiovascular toxicity generally can be improved by correction of the hypotension and acidosis, patients with serious arrhythmias may require administration of an antiarrhythmic drug. For tachyarrhythmia with QRS prolongation, class I and III antiarrhythmics should be avoided as they can aggravate the "quinidine-like" effect and prolong the repolarization effect of TCAs (Burrows et al., 1976; Sasyniuk et al., 1986; Kerr et al., 2001). Instead, class II antiarrhythmics, including propranolol, would be more beneficial considering the catecholamine reuptake inhibition effect of TCAs (Brackenridge et al., 1968). However, these beta-adrenergic blockers have the potential to depress myocardial contractility, and so they may further decrease the cardiac output and blood pressure (Kerr et al., 2001). Most importantly, sufficient cardiopulmonary resuscitation time with close monitoring are very important in TCA toxicity cases, as several cardiac arrest patients survived after 3-5 hours of external cardiac massage and ventilator (Southall and Kilpatrick, 1974; Abeyaratne et al., 2016).

Other side effects of TCAs, such as metabolic and electrolyte disturbances, especially magnesium and potassium, should also be corrected. Magnesium sulfate administration for myocardial stabilization and early after-depolarization suppression is suggested in humans (Kan et al., 2014). Correction of hypokalemia is also crucial, especially in patients with prolonged QT intervals. The central nervous system side effects of TCAs usually present as self-limiting seizures. However, in patients with recurrent seizures, benzodiazepines and barbiturates are drugs of choice (Kerr et al., 2001; Verbree et al., 2016).

Conclusion

In conclusion, amitriptyline is relatively effective in NP management but it can produce clinical side effects, including mental alteration and various cardiovascular disturbances, even at a low dose when prescribed to high risk patients. Therefore, using amitriptyline in at-risk cases, most importantly those that are aging or with cardiovascular comorbidity or liver function deficiency, requires thorough physical examination throughout the treatment, while cardiovascular function evaluation, including ECG and blood pressure monitors, should also be routinely performed to evaluate any acute adverse effect, and to predict the physiological alteration induced by chronic TCAs treatment.

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บทคัดย่อ

ความเป็นพิษต่อหัวใจและหลอดเลือดของยาอะมิทริปไทลีน ในการรักษาอาการปวดเหตุประสาทในสุนัข

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ในภาวะปัจจุบัน อายุขัยของสัตว์เลี้ยงยืนยาวขึ้นเนื่องจากการพัฒนาของการดูแลสัตว์เลี้ยงโดยสัตวแพทย์ ทำให้ปัญหาที่เกี่ยวข้องกับความเสื่อมตามอายุจึงเพิ่มขึ้นตามมา และเป็นที่รู้กันว่าความผิดปกติของระบบประสาทเป็นปัญหาที่เกิดได้ทั้งจากความเสื่อมตามอายุ และรอยโรคจากสาเหตุต่าง ๆ ซึ่งในหลายกรณีมักจะพบอาการปวดเหตุประสาท (neuropathic pain) ตามมา ซึ่งอาการนี้ส่งผลกระทบอย่างมากต่อผลทางคลินิกและคุณภาพชีวิต แต่การตรวจหาสาเหตุที่จำเพาะของอาการนี้ในผู้ป่วยแต่ละรายนั้นทำได้ยาก จึงทำให้การวางแผนการรักษามักอาศัยข้อมูลจากอาการที่ตรวจพบ และผลจากการทดลองรักษาที่ได้รับการยอมรับ โดยยาที่นิยมนำมาใช้ในการรักษาอาการนี้เป็นอันดับแรก ๆ คือ ยาอะมิทริปไทลีน (amitriptyline) ที่เป็นยาแก้ซึมเศร้ากลุ่มไตรไซคลิก (tricyclic antidepressant) ที่มีผลหลายอย่างต่อตัวรับของสารสื่อประสาทและช่องไอออนต่าง ๆ อย่างไรก็ตามผลของยาตัวนี้ยังขึ้นกับหลายปัจจัย เช่น ปริมาณยาที่ได้รับ ประสิทธิภาพของร่างกายด้านเมแทบอลิซึมของยา โรคต่าง ๆ ที่มีอยู่ และการตอบสนองของเซลล์ต่อยา นอกจากผลทางการรักษา ยาอะมิทริปไทลีนยังสามารถก่อผลข้างเคียงต่าง ๆ โดยเฉพาะความเป็นพิษต่อหัวใจและหลอดเลือด อย่างไรก็ตามข้อมูลด้านความเป็นพิษต่อหัวใจและหลอดเลือดในทางการสัตวแพทย์ยังมีค่อนข้างน้อย คณะผู้เขียนจึงได้ทำการรวบรวมและวิจารณ์ข้อมูลเกี่ยวกับการใช้ยาอะมิทริปไทลีนเพื่อการรักษาอาการปวดเหตุประสาท และความเป็นพิษต่อหัวใจและหลอดเลือดที่เกี่ยวข้องจากสิ่งตีพิมพ์ทั้งในของมนุษย์และสัตว์ไว้ในบทความวิชาการนี้ โดยหวังว่าข้อมูลเหล่านี้จะช่วยเน้นถึงความสำคัญของการตรวจประเมินระบบหัวใจและหลอดเลือดเมื่อมีการใช้ยาอะมิทริปไทลีน

คำสำคัญ: อะมิทริปไทลีน สุนัข ความเป็นพิษต่อหัวใจและหลอดเลือด อาการปวดเหตุประสาท

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