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Reviews

Dissociative anaesthesia in dogs and cats with use of tiletamine and zolazepam combination. What we already know about it

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Abstract

This article is an attempt to gather available literature regarding the use of tiletamine and zolazepam combination in anaesthesia in dogs and cats. Although tiletamine and zolazepam mixture has been known in veterinary practice for a long time, the increased interest in these drugs has been observed only recently. Tiletamine, similarly to ketamine, is a drug which belongs to the phencyclidine group. Ketamine has considerable popularity in veterinary practice what suggests that other dissociative anaesthetic drugs, such as tiletamine, could also prove effective in cats' and dogs' anaesthetic care. Zolazepam is a widely used benzodiazepine known for its muscle relaxant and anticonvulsant properties. While conducting an electronic search for articles regarding the use of tiletamine-zolazepam combination in dogs and cats, it has been discovered that the literature on the subject (tiletamine-zolazepam combination in dogs and cats) is quite scarce. Very few articles were published after 2010. Databases used were: Google Scholar, Scopus, PubMed. Most of the adverse effects, including those affecting the cardiovascular, nervous, and respiratory systems, were strictly dose-dependent. Tiletamine-zolazepam combination can be safely used as a premedication agent, induction for inhalation anaesthesia, or an independent anaesthetic for short procedures. Contraindications using tiletamine-zolazepam mixture include central nervous system (CNS) diseases such as epilepsy and seizures, head trauma, penetrative eye trauma, cardiovascular abnormalities (hypertrophy cardiomyopathy in cats, arrhythmias or conditions where increase of heart rate is inadvisable), hyperthyroidism, pancreatic deficiencies or kidney failure.

Keywords: anaesthesia, cat, dissociative anaesthesia, dog, tiletamine-zolazepam

Introduction

According to the datasheet's producer of Zoletil® (Virbac, Carros, France), it is a non-opioid, non-barbiturate injection anaesthetic – combination of equal concentrations of tiletamine and zolazepam (50 milligrams per milliliter (mg/ml) tiletamine and 50 mg/ml zolazepam or 25 mg/ml tiletamine and 25 mg/ml zolazepam) in 1:1 ratio. Tiletamine is a phencyclidine derivative and works as a dissociative anaesthetic. It differs from ketamine in a longer duration and a greater analgesic effect (Lin et al. 1993). Zolazepam is a benzodiazepine sedative chosen to be combined with tiletamine due to its effective anticonvulsant and muscle relaxant properties. Because it belongs to the benzodiazepine group of drugs, zolazepam could also induce anxiolysis, sedation, and hypnosis (Maddison et al. 2008). The combination of tiletamine and zolazepam has proven to have the following effects:

- muscle stiffness without the stimulation effect shortly after administration, followed by moderate relaxation of muscle tissue,
- immediate and moderate visceral and somatic analgesia
- general anaesthesia with muscle relaxation, maintaining the laryngeal, palpebral, and pharyngeal reflexes without the occurrence of bulbar palsy (Thurmon et al. 1996).

The combination of tiletamine and zolazepam can either induce anaesthesia or sedation, depending on the dose and route used. Low doses (Table 1) of the tiletamine-zolazepam combination were tested for sedation in dogs with a duration of action of about 22 min (Donaldson 1989). Tiletamine - zolazepam is also suitable as a premedication in dogs at doses of 3 mg/kg administered as an intramuscular injection (IM) (Cullen and Reynoldson 1997). In cats, Ilkiw showed that the possible route of premedication with tiletamine - zolazepam is subcutaneous (SC) at a dose of 2.5 mg/kg (Ilkiw 1992). The same author reported that intubation was found easy after administration of tiletamine-zolazepam at 9.7 mg/kg IM (Ilkiw 1992). Although tiletamine-zolazepam combination is meant to be injected intramuscularly or intravenously in cats and dogs, as per the manufacturer's advice, there are studies conducted on cats and dogs, where the drug was administered via the oral mucosa (buccal administration) (Huang et al. 2017, Nejamkin et al. 2020). This way of administration, however, is not included in the producer's product characteristics leaflet. Sedative effect of Zoletil®/Telazol® (Zoetis, Kalamazoo, US) has been described by the manufacturer as sufficient for treatments accompanied with mild or moderate pain level (Arrijoja-Dechert 1997).

According to Zoletil® datasheet's producer, for short and painless surgical procedures in dogs after premedi-

cation, the dosage starts from 5 mg/kg IV. For painful procedures, the effective dose is 10 mg/kg IV. In cats, 5 mg/kg IV is enough for short and for not very painful procedures.

The duration of anaesthesia in both species is dose-dependent and ranges from 20 to 60 min after a single injection (IM or IV). Full dose should not exceed 26.4 mg/kg IV in both species (according to Zoletil® datasheet's producer).

On the European Union (EU) market, tiletamine-zolazepam combination is not a controlled substance and is approved for IV or IM administration. In Europe, tiletamine-zolazepam combination is known under the manufacturer's name of Zoletil® and is registered for veterinary anaesthesia in dogs and cats. It is distributed as a lyophilisate and a solvent. After reconstitution, it should be a clear, colourless to greenish or yellowish solution, free from particles and it can be stored for 24 hours at a temperature between 2°C and 8°C.

The main goal of this article is to present current literature on the influence of tiletamine and zolazepam mixture (combination) on specific organ systems in dogs and cats.

Pharmacology

Tiletamine [2-ethylamino-2-(2-thienyl) cyclohexanone] is an arylcyclohexylamine related to phencyclidine and ketamine in structure (Cording et al. 1999). It is a potent ligand at the PCP-binding site of the N-methyl-D-aspartate (NMDA) receptor and is pharmacologically classified as a noncompetitive NMDA receptor antagonist. Like other drugs in the phencyclidine class, tiletamine produces dissociative anaesthesia (Guarda et al. 2007, Saha et al. 2007).

The state of dissociative anaesthesia induced by these drugs is characterised by the dissociation of the limbic system and thalamus, which has been proven by electroencephalographic (EEG) examination (Lin et al. 1993). This phenomenon is most probably caused by interrupting the ascending transmission from the unconscious to the conscious parts of the brain, rather than by general depression of all brain centres (Corssen et al. 1968). Phencyclidine drugs cause immobilisation and tranquilisation as well as general anaesthesia when higher doses are used (Thurmon et al. 1972).

Tiletamine-zolazepam combination is meant to be injected intramuscularly or intravenously in cats and dogs, as per the manufacturer's advice. However, there are studies conducted on cats and dogs, where the drug was administered via the oral mucosa (buccal administration) (Ramsay and Wetzel 1998, Huang et al. 2017, Nejamkin et al. 2020), although this way of administration is not included in the producer's product character-

ristic leaflet. Sedative effect of Zoletil®/Telazol® has been described by the manufacturer as sufficient for treatment accompanied with mild or moderate pain levels (Arrijoja-Dechert 1997).

There are relevant differences in the pharmacokinetics of both tiletamine and zolazepam in dogs and cats, which impact the clinical effect after drug administration in those two species. That is why it is important to consider the pharmacokinetics for each one separately. In both cases, the peak serum concentration of tiletamine is achieved 30 min after IM administration of 10 mg/kg (according to the datasheet's producer), however, it reaches a pharmacological half-life in dogs after around 75 min and in cats after 150-240 min. Tiletamine's complete elimination from dogs occurs after around 8 hours and is a result of intensive breakdown of the drug in the liver to two metabolites which are later excreted in urine. Only 4% of tiletamine is excreted in its original form. In felines, however, the elimination time is around 48 hr and is a result of a breakdown to 3 metabolites which are excreted in urine. Tiletamine is not excreted in faeces in cats (Thurmon et al. 1996).

An earlier study reported that treatment of rats with ketamine, a dissociative anaesthetic structurally related to tiletamine, produces an inductive effect on cytochrome P450 that is similar to that of phenobarbital (Marietta et al. 1977). Ketamine metabolism in dogs is performed by cytochrome P450 enzyme (CYP) (Mössner et al. 2011). The general CYP inhibitor 1-aminobenzotriazole almost completely blocked ketamine metabolism in human and canine liver microsomes but not in equine microsomes (Mössner et al. 2011). There are no reports of the effects of zolazepam, a benzodiazepine derivative, on hepatic cytochrome P450 (Wong and Bandiera 1996).

Zolazepam [4-(2-Fluorophenyl)-1,3,8-trimethyl-6,8-dihydropirazolo[3,4-e]-diazepin-7-one] - acts as a positive allosteric modulator of the gamma-aminobutyric acid (GABA) A receptor (Saha et al. 2007, Pattanapon et al. 2018).

Zolazepam, as the second component of Zoletil®/Telazol® drug, reaches its peak plasma concentration in both cats and dogs 30 min after the administration of 10 mg/kg IM (according to the datasheet's producer). Its elimination half-life, although, is 60 min or less in dogs and approximately 270 min in cats. The effect of this difference can be observed during anaesthetic recovery - dogs are under the influence of tiletamine without balancing effects of zolazepam for a longer time. In both species, zolazepam is metabolised in the liver and excreted mostly in urine and, in a small fraction (3%) in faeces (Thurmon et al. 1996).

The available literature lacks information on the specific metabolic pathways of tiletamine and zolazepam in the liver of dogs and cats. However, studies have been

performed on other animal species. Following in vitro incubation with equine liver fraction S9, a number of metabolites were successfully detected for tiletamine and zolazepam (Fenwick and Scarth 2011). Three metabolites of zolazepam and one metabolite of tiletamine were identified in pig's urine, plasma and in microsomal incubation (Kumar et al. 2014). Moreover, tiletamine, its metabolite, and zolazepam were detected in the urine of a 22-year-old man who died of an overdose of drugs (Chung et al. 2000). Another patient, who also died from acute mixed drug intoxication, had tiletamine and zolazepam in his blood, urine, and liver and ketamine in his blood and urine (Cording et al. 1999).

Anaesthetic induction and recovery

Most of the research focused on the quality of anaesthesia induced with Zoletil®/Telazol® presents unified results. The combination of tiletamine and zolazepam provides good induction, smooth transition to vertical position, and dose-dependent sedative effect. Side effects like hyperactivity (restlessness), hypersalivation, or catatonia have been rarely observed (Hellyer et al. 1989, Savvas et al. 2005, Krimins et al. 2012).

Both authors' experience and studies suggest that the post-anaesthetic recovery process, in most cases, had a mild course, although significantly longer compared to standard protocols based on propofol. In some of the patients, the process of regaining consciousness was rapid, with symptoms like those described in humans as hallucinations, e.g., paddling, vocalization, euphoria with no reaction to human. All of them were reactions depending on the dose as well as on the animal's temperament (Hampton et al. 2019). Moreover, the time needed to regain consciousness or attain sternal recumbency (followed by standing) depends on the dosage, with higher doses causing a visibly prolonged recovery period. It is possible for the animal to experience restlessness, excitement, or hallucinations, all of which are dose-dependent symptoms (Hellyer et al. 1989, Pablo and Bailey 1999, Savvas et al. 2005, Krimins et al. 2012, Nejamkin et al. 2020). During recovery, more often in dogs than in cats, the following side effects are observed: excitement, purposeless muscle activity, and hyperthermia. Additionally, the quality of recovery is reduced and the time of recovery is prolonged when high or repeated doses are used (Maddison et al. 2008).

Anaesthesia induced only with Zoletil®/Telazol® causes rapid return to consciousness in dogs, as well as head swaying, vocalization, involuntary muscle twitching, muscle stiffness and hypertonia (Short 1989, Lin et al. 1991, Pablo and Bailey 1999, Caulkett et al. 2000). Based on the conducted research, a decrease

in brain activity during the regaining of consciousness in dogs was observed after using the xylazine-Zoletil® mixture (Jang et al. 2004). However, medetomidine in combination with Zoletil® proved to be less effective in the patient's smooth return to consciousness than the combination of xylazine with Zoletil® (Jang et al. 2004).

Cardiovascular system

The influence of tiletamine and zolazepam combination on the cardiovascular system strictly depends on the dose. Both intramuscular and intravenous administration can lead to cardiac rhythm abnormalities – including sinus tachycardia or premature ventricular contractions. These abnormalities are caused by the influence on the direct depression of baroreceptors resulting in a reflex increase in sympathetic tone (Hellyer et al. 1988). It has been observed that intramuscular administration of 10 mg/kg dose in dogs would lead to sinus tachycardia causing a decrease in cardiac ejection fraction with no influence on cardiac output (Short 1989). Higher doses of 20 mg/kg, administered intramuscularly in dogs, resulted in sinus tachycardia with a simultaneous significant cardiac output decrease (Short 1989).

After the administration of 5 mg/kg IV in dogs, heart rate increased significantly by around 94.9% from baseline and returned to the baseline values after 60 min (Hampton et al. 2019). On the other hand, other studies showed that the induction of anaesthesia with 5 mg/kg IV caused no changes either in heart rate (HR) or in the cardiac output, as observed by the researchers (Pattanon et al. 2018).

Blood pressure changes are also frequently observed. Both higher and lower doses of tiletamine combined with zolazepam can result in a decrease of systolic pressure. With the dose of 10 mg/kg IM in dogs, the drop of systolic pressure is minimal and constant until anaesthetic recovery, sometimes with a coexisting increase of diastolic pressure (Arrijoja-Dechert 1997). When using higher doses, e.g., 20 mg/kg IM, in the same species, lowered blood pressure and decreased cardiac contractility were observed (Arrijoja-Dechert 1997). After using 5 mg/kg IV, the decrease in systolic arterial pressure (SAP), mean arterial pressure (MAP), and diastolic arterial pressure DAP values was noted (Hampton et al. 2019). Pattanon et al. showed that the dose of 5 mg/kg IV in dogs caused a slight decrease in blood pressure but within a normal range. The results of their study show that tiletamine-zolazepam mixture at that dose caused an increase in HR and influenced the parasympathetic activity. This conclusion was made based on the measurement of the standard deviation of the N-N intervals made by researchers (Pattanon et al. 2018).

Other studies conducted on dogs concluded that using three different doses of tiletamine and zolazepam combination (6.6, 13.2, and 19.8 mg/kg IV) also resulted in hemodynamic changes including a significant increase in heart rate and cardiac output with an accompanying decrease in vascular resistance and blood pressure (Hellyer et al. 1989).

In cats, no changes in heart rate were observed after intramuscular and intravenous administration of Zoletil®/Telazol® (Hellyer et al. 1988, Arrijoja-Dechert, 1997). Pablo and Bailey (1999) suggest that after using IV doses of 9.7, 15.8, and 23.7 mg/kg, the blood pressure, peripheral vascular resistance, and contractility increased above the baseline values and then decreased slightly within 5 min. When lower doses were used (9.7-15.8 mg/kg), a slight drop in blood pressure occurred (Caulkett et al. 2000). A decrease in cardiac output was observed when using higher doses (above 15 mg/kg IV) (Hellyer et al. 1988).

The differences in the impacted hemodynamic parameters in the studies mentioned above may arise from various pre-anaesthetic protocols. In conclusion, tiletamine and zolazepam combination allows maintaining a stable hemodynamic state in patients, especially in lower doses (under 10 mg/kg in both species). Higher doses (above 15 mg/kg in dogs and cats) proved to have a significant depressing effect on the cardiovascular system, mainly through decreased cardiac contractility, lowered cardiac output, and lowered blood pressure.

Nervous system

The effect of tiletamine on the central nervous system is highly dependent on the species. At low doses, it caused excitement and ataxia in mice and rats, which was not observed in other animal species. When moderate doses were used, catalepsy occurred in all species. Surgical anaesthesia was induced in cats and monkeys at high doses. In dogs, light anaesthesia or transitory clonic seizures were induced using high doses (Chen et al. 1969). The effects of tiletamine on the central nervous system (CNS) are closely related to the dose. Patients' eyes remain open, corneal reflex is present, and muscle relaxation and analgesia are not sufficient for surgery, therefore, additional analgesics are recommended. Following the administration of a nearly lethal dose of tiletamine (150 mg/kg intramuscularly to cats), short and mild clonic convulsions were observed (Lin et al. 1993). However, when a 20 mg/kg dose of tiletamine was administered intravenously in dogs, anaesthesia and analgesia were achieved in some patients, while others developed convulsions (Lin et al. 1993). The combination of tiletamine with zolazepam leads to rapid

Table 1. Table shows suggested doses, purpose, species, route and duration after administration of tiletamine-zolazepam combination.

Dose	Purpose	Species	Route	Duration	References
2-4 mg/kg**	sedation/ premedication	dogs	IV, IM, S.C.	about 20 min	Donaldson 1989, Ilkiw 1992, Cullen 1997
5 mg/kg*	induction of general anaesthesia	dogs, cats	IV, IM	20-60 min	Jang 2015, Pattanapon 2018, Hampton 2019
10 mg/kg*	induction of general anaesthesia	dogs, cats	IV, IM	20-60 min	Hellyer 1989, Short 1989, Arrijoja-Dechert 1997, Jang 2015
20 mg/kg*	induction of general anaesthesia	dogs, cats	IV, IM	up to 60 min	Arrijoja-Dechert 1997, Jang 2015

* Doses from 5 to 20 mg/kg could lead to sinus tachycardia with or without changes in cardiac output. ** Doses recommended after proper premedication for induction of general anaesthesia.

cataplexy, which then disappears and gives myorelaxation. Tiletamine-zolazepam causes moderate analgesia of internal organs with preservation of the laryngeal, palpebral, and pharyngeal reflexes, without the presence of bulbar palsy. Lin et al. also wrote about the possibility of hypersalivation in most animals (Lin et al. 1993). At the dose recommended by the producer of Zoletil® (5-25 mg/kg IV), loss of sensory perception and consciousness is achieved, however, without entering a state of deep hypnosis.

Tiletamine can increase intracranial pressure (ICP), cerebral blood flow, and metabolic oxygen requirements of the brain (Maddison et al. 2008). This is the main reason why tiletamine-zolazepam should not be used in patients with raised ICP and cerebral disease. Moreover, in case of epilepsy and myelography, tiletamine should be administered with caution (Maddison et al. 2008).

In inflammation, cancer, neurodegenerative disorders, and pain, the main factor is adenosine 5'-monophosphate (AMP) activated protein kinase (AMPK) (Giordanetto and Karis 2012). This activator has the great influence on sensory neurons in culture, modulating signalling pathways as well as excitability (Price and Dussor 2013). The increase of the phosphorylation of AMPK (provide to the inhibition of AMP) in rats can be induced by both tiletamine as well as xylazine (Shi et al. 2016).

Tiletamine potently antagonizes NMDA-induced biochemical and electrophysiological responses in a non-competitive manner (Klockgether et al. 1988). By blocking NMDA receptors, tiletamine inhibits pain signalling and has an analgesic effect. In addition, as a widespread receptor in the CNS, it plays a key role in neurogenesis (Pelissier et al. 2008).

In the study conducted by Li-Xue Su et al. tiletamine has been shown to reduce eIF4E-binding protein 1 (4EBP1) mRNA levels in the brain in rats (Su et al. 2017). This information suggests that the anaesthetic may reduce neuronal activity to induce sedation by

decreasing expression of the eIF4E-binding protein 1 (4EBP1) gene (Su et al. 2017). The effect of tiletamine on the expression of liver kinase B1 (LKB1), activated AMPK (AMPK α), and 4EBP1 may partly underline the pharmacological action of the drug (Su et al. 2017).

In addition, tiletamine, as a noncompetitive N-methyl-D-aspartate antagonist, causes an increase or absence of changes in brain glucose metabolism when compared to the patient's full consciousness, contrary to propofol and isoflurane which reduce brain glucose metabolism (Momosaki et al. 2004, Itoh et al. 2005).

Tiletamine-zolazepam should not be used in patients with central nervous system signs or with head trauma present due to the fact that tiletamine increases blood flow in brain and cerebellum as well as brain oxygen consumption (Pablo and Bailey 1999, Lumb et al. 2007).

In a study conducted by Fujikawa ketamine also has neuroprotective effects as a drug that blocks N-methyl-D-aspartate receptors (Fujikawa 2019). Popik et al. compared the effects of ketamine and tiletamine, proving that they both induce an antidepressant as well as anti-obsessive-compulsive effect in mice (Popik et al. 2017). Additionally, zolazepam has an anticonvulsant, but does not have analgesic properties. This suggests that the combination of tiletamine and zolazepam is complementary.

Ophthalmology

Anaesthesiologists should carefully choose an appropriate anaesthetic protocol for ophthalmic patients. Changes of intraocular pressure (IOP) during the anaesthetic period are not desirable in patients with ophthalmic disease (Duke-Novakovski et al. 2016). Rapid increase of IOP can cause severe complications, especially in patients with near-perforating corneal lesions or glaucoma (Hofmeister et al. 2009). Due to the effects of anaesthetic drugs on the central nervous, respiratory, and circulatory systems, most of them reduce or maintain IOP (Hahnenberger 1976, Johnson et al. 2008,

Gelatt et al. 2011). For instance, ketamine and midazolam combination had no significant effect on IOP in dogs, but after an IV administration of ketamine only a substantial increase in IOP was observed. Less substantial, but still significant, increase of IOP was noticed after the injection of diazepam only (Ghaffari et al. 2010, Kovalcuka et al. 2013). Moreover, after the induction of anaesthesia with propofol or alfaxalone, a potentially clinically significant increase in IOP followed (Hasiuk et al. 2014). Different anaesthetic drugs can either increase extraocular muscle tone or change the rate of aqueous production and/or outflow (Gelatt et al. 2011). This is how the IOP can change.

Jang M. et al. and other authors showed that intravenous administration of tiletamine – zolazepam in dogs (tab.1) did not cause a significant increase in IOP, contrary to the ketamine - diazepam combination which induced a significant IOP increase (Hofmeister et al. 2009, Kovalcuka et al. 2013, Jang et al. 2015). Moreover, Hahnenberger said that tiletamine-zolazepam administration at the dose of 2 mg/kg IM in cats had no significant effect on IOP, but after administration a higher dose (4 mg/kg IM) a minimal effect on IOP was observed (Hahnenberger 1976). The reason for this is the minimal impact of tiletamine on the contraction of the extraocular muscles and/or the masking effect of tiletamine-induced growth of IOP by zolazepam (Hahnenberger 1976, Artru 1991, Lumb et al. 2007). Tiletamine-zolazepam is an appropriate anaesthetic combination for dogs with ophthalmic problems, in which the increase of IOP is not desired (Jang et al. 2015). Studies conducted on cats revealed that the combination of intranasal and intramuscular tiletamine-zolazepam showed no significant impact on IOP (Yanmaz et al. 2016).

Respiratory system

Most of the research on the effects of tiletamine-zolazepam combination on the respiratory system in dogs is consistent. After its administration, a notable drop in spontaneous breath in cats and dogs can be observed and the effect lasts as long as the drug is working (around 60 to 90 min) (Short 1987, Ko et al. 2007).

When Zoletil®/Telazol® was combined with other sedatives, such as opioids or alpha-2-agonists, no notable impact on the respiratory system was observed in dogs. The tiletamine-zolazepam-butorphanol-medetomidine combination proved to have no depressing effect on the respiratory system (Ko et al. 2007). When combined with xylazine, an initial increase followed by a decrease in respiratory rate was noted, which increased again during the final stages of anaesthesia (Lu et al. 2014).

In cats, no changes in the respiratory rate were observed after an IV administration of low (9.7 mg/kg) or medium (15.8 mg/kg) doses of the tiletamine-zolazepam mixture. High doses (23.7 mg/kg) applied intravenously were shown to significantly decrease the respiratory rate (Hellyer et al. 1988).

Although apnea after intravenous administration is possible, it is observed relatively rarely. In Savvas et al. research, one out of six patients had shown symptoms of apnea 1 min after induction (5 mg/kg IV) of anaesthesia. In those patients, apnea lasted for about 70 sec (Savvas et al. 2005). In a different research, apnea was observed after applying a dose of 2 or 4 mg/kg intravenously with no prior premedication (Donaldson 1989). Higher doses (9.9 mg/kg IV) triggered apneustic breathing in one in every 10 canine patients (Tracy et al. 1988). Most of the publications mention significant changes in oxygen Saturation (SpO₂) in the first 5 to 20 min of anaesthesia (Hellyer et al. 1988, Pablo and Bailey 1999, Savvas et al. 2005, Ko et al. 2007). In the above-mentioned studies, there is only one paper stating that the dogs were intubated and received oxygen supplementation (Hellyer et al. 1988). In a study conducted on dogs after IV administration of tiletamine-zolazepam at a 5 mg/kg dose, researchers mentioned that respiratory acidosis occurred (Savvas et al. 2005). An increase in H⁺ over 50 nanomole per litre (nmol/L) and partial pressure of carbon dioxide (PaCO₂) over 5.99 kilopascals was observed after IV and IM administration of tiletamine-zolazepam at the doses of 5 mg/kg and 10 mg/kg (Savvas et al. 2005). Hypercapnia was noted in the first 4 min after induction of anaesthesia and usually returned to baseline values by the end of the anaesthetic procedure (Savvas et al. 2005). In another study conducted on dogs, after the induction of anaesthesia with tiletamine-zolazepam at the dose of 5 mg/kg IV, only one out of six dogs showed postinduction apnea. No hypoxemia was detected after induction, however, a significant increase in respiratory rate was noted in the first 10 min of the study (Hampton et al. 2019).

Side effects and contraindications

As mentioned earlier in the nervous system section, the tiletamine-zolazepam combination should not be used in patients with central nervous system disease or present head trauma because tiletamine increases blood flow in the cerebellum as well as brain oxygen consumption. (Pablo and Bailey 1999, Lumb et al. 2007).

Due to their positive chronotropic effect, Zoletil and Telazol should not be used in cats suffering from hypertrophic cardiomyopathy. In these cases, as well as in patients suffering from hyperthyroidism, it is impor-

tant to avoid the increase of HR and cardiac output (Ilkiw 1992, Pablo and Bailey 1999, Duke-Novakovski et al. 2016). The drug is also not recommended for patients with arrhythmia and penetrative eye trauma.

Kidney failure is another contraindication due to the fact that a small fraction of the drug is excreted in its unchanged form in urine (Ilkiw 1992). In cats, after the hepatic metabolism occurs, almost all metabolites of the drug are excreted by the kidneys (Lumb et al. 2007), which can significantly aggravate the patient's condition in the postoperative period.

It is not advised by the producers to use Zoletil®/Telazol® after premedication with phenothiazine drugs, as they induce vasodilatation and have a depressive effect on the heart. However, this effect is strictly dose-dependent and studies have established a successful anaesthetic protocol using this combination (Fieni F. 1989, Lacerda et al. 2010).

Due to the fact that dogs have a more violent arousal and cats have a prolonged time of action, tiletamine – zolazepam combination is not recommended for anaesthesia during long procedures as it requires repetition of doses (Caulkett et al. 2000). However, it is possible to use this combination as a premedication agent or for induction of general anaesthesia prior to maintenance with inhalant agents for long surgical procedures.

Due to increased salivation caused by zolazepam-tiletamine combination, the use of anticholinergic drugs (e.g., atropine or glycopyrrolate) may be required (Short 1989, Arrijoja-Dechert 1997). If the patient is intubated with the airway properly secured, hypersalivation is not considered a problem (Pablo and Bailey 1999). However, if using anticholinergic drugs, its stimulating effect on the heart rate should be considered and monitored with care.

Antagonistic drugs

Because Zoletil®/Telazol® are compound drugs, they do not have a direct antagonist. Therefore, both substances (tiletamine and zolazepam) should be considered separately.

Nowadays, the only choice available on the market as an antagonistic drug for zolazepam is flumazenil. Flumazenil is a highly selective, competitive antagonist of GABA receptors, and its biological half-life is maximum 1 hr. After its intravenous administration, flumazenil is distributed to the tissues and relatively quickly reverses the sedative and myorelaxant effects of benzodiazepines (Lumb et al. 2007). Administered in dogs at a dose of 0.1 mg/kg 20 min after the application of Zoletil®/Telazol® (10 mg/kg IV), it significantly accelerated the time of arousal, return to sternal recumbency and the time needed for the animal to stand up and

begin walking (Won et al. 2010). Indirect adverse effects of flumazenil administration, such as seizures or muscle rigidity, might appear if the drug is given too soon after the administration of tiletamine. Because flumazenil may reverse the effect of zolazepam but not the effect of tiletamine, it is recommended for the benzodiazepine antagonist to be administered at least 20 min after the last dose of dissociative anaesthetic (Won et al. 2010).

The use of atipamezole as an alpha-2 adrenoceptor antagonist in anaesthetic protocols based on tiletamine-zolazepam combination (10 mg/kg) as well as medetomidine (0.25 mg/kg), might have a positive impact on the process of waking up in cats (Kim et al. 2007). Atipamezole should be administered intramuscularly, 20 min after the induction of anaesthesia (Kim et al. 2007). Research by Ko et. al. (2007) suggests that doxapram administered intramuscularly (5.5 mg/kg) increases respiratory rate and shortens the waking up time when combined with tiletamine/zolazepam. This suggests that doxapram could potentially be used as an antagonist for the zolazepam-tiletamine mixture (Ko and Berman 2010). It should be used with caution in patients where an increased HR or CNS stimulation along with the effects of Zoletil®/Telazol® could be contraindicated because of its cardiovascular and CNS stimulant effects.

Conclusion

Zoletil®/Telazol® is a drug that is useful in preanesthetic, sedative, and anaesthetic procedures. Considering all the research presented in the article, the authors are confident that the tiletamine-zolazepam combination is a drug that is safe and useful in everyday veterinary practice in cats and dogs.

The route of administration affects time, quality of anaesthesia, sedation level, and analgesic effect. Based on the authors' experience, the recommended dosage of Zoletil®/Telazol® ranges from 1 to 7.5 mg/kg IV in dogs after premedication with an α_2 – adrenergic receptor agonists with or without opioids, and from 5 to 20 mg/kg IM without any pre-medication or 5 to 15 mg/kg with proper premedication. In cats, we would recommend doses from 2 to 5 mg/kg IV after premedication with α_2 - adrenergic receptor agonist with or without opioids. There are no premedication agents that should be avoided.

Its effects on respiratory and cardiovascular systems are dose-dependent. Only when higher doses (20 mg/kg) of Zoletil®/Telazol® were administered, major downfalls in heart rate and in blood pressure occurred; nevertheless the tiletamine-zolazepam combination is safe and predictable in its action.

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