Scientific Works. Series C. Veterinary Medicine. Vol. LXVIII (2), 2022
ISSN 2065-1295; ISSN 2343-9394 (CD-ROM); ISSN 2067-3663 (Online); ISSN-L 2065-1295

CHANGES OF METABOLIC LIVER PARAMETERS ASSOCIATED WITH GENERAL ANESTHESIA IN DOGS AND CATS – A REVIEW

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Abstract

The aim of this systematic review is to examine the effects of different anesthetic drugs and protocols on hepatic functions. The liver is a very important organ since it is directly involved in biotransformation of the drugs used in anesthesia. Comprehensive understanding of anesthetic drugs and their effects on hepatic functions remains fundamental to a successful anesthesia. Understanding the connections that exist between anesthetic drugs and liver function remains essential for a safe anesthesia both during the surgery and in the post-operative period. Almost all anesthetic drugs depend on hepatic biotransformation into their metabolites that can be transported and excreted by the kidneys. If the liver enzymes are altered, the biotransformation of the drugs will be decreased and the recovery from the anesthesia prolonged

Key words*: anesthesia, biotransformation, enzymes, liver.*

INTRODUCTION

Through this study, the effects of different anesthetic drugs and protocols on liver function will be described.

The liver is located between the diaphragm and the abdominal viscera. The blood that arrives from the gastrointestinal tract is full of proteins, carbohydrates, fat and other exogenous particles (drugs, bacteria). From the total cardiac output, 25-30% flows through the liver via dual blood supply: the hepatic artery and the portal vein. The main function of the liver is to participate to nutrients digestion by breaking them down to more absorbable substances. The other functions of the liver that are more important for the anesthesist are the homeostasis of glucose, production of proteins needed for coagulation, production of albumin and other proteins needed to maintain the plasma oncotic pressure, biotransformation and excretion of drugs and ammonia removal and blood urea nitrogen (BUN) production (Tranquilli, 2013; Dugdale 2020). The functional unit of the liver is the hepatic lobule. These lobules are hexagonally shaped and are organised around the central vein. Histologically, the hepatocytes can be divided into three different areas based on their localisation. First area is located at the periphery, closer to the portal canals and arterial blood vessels. The hepatocytes in zone one receives the highest amount of oxygen and also is the area where most oxidative processes occur. Zone two is a transitional zone between zone one and zone three. Zone three is closer to the central vein, hence the hepatocytes receive less amount of oxygen. These hepatocytes contain a large number of organelles responsible for drug deactivation and metabolism (Pawlina, 2018).

BIOTRANSFORMATION AND ELIMINATION OF XENOBITICS

Xenobiotic is a general term used to describe a chemical substance that is foreign to the animal body. There are a lot of substances that can be included here, such as drugs, pesticides, food additives (Patterson et al., 2010). The enzymatic system that is involved in the biotransformation of drugs is mainly localized in the liver, although there are also other organs capable of biotransformation. The majority of anesthetic drugs are removed from the blood by

hepatocytes and excreted in the bile or urine. Drugs usually undergo a two-phase process in order to became an easily excreted substance. In phase one, the drugs undergo an oxidation reaction so that one or more hydroxyl groups are attached to the molecule. By doing this, the more lipophilic compounds are converted intro hydrophilic compounds so that they can be excreted via bile or urine. The main class of enzymes responsive for these reactions belongs to the family of cytochrome P450 monooxygenases (Reece et al., 2015). Ketamine has a reversible and competitive influence on the CYP 3A family, but also these effects may be due to the metabolite, norketamine (Meneguz et al.,1999). Because there are a lot of enzymes in the P450 family, it is very important to know which enzyme reacts with different drugs. In one investigation, the metabolism of ropivacaine was studied. In general, local anesthetics are administrated with other agents, including general anesthesia. When there are metabolized by the same P450, some agents may influence the plasma concentration of ropivacaine (Oda et al.,1995). Differences between CYP 450 exist not only among species, but also among breeds and genders. One drug take into consideration is propofol. Greyhounds have a slower drug clearance and longer recovery compared with any other breeds. This may be to the fact that the enzyme activity are almost three times lower in greyhounds compared with beagle microsomes (Hay Kraus et al., 2000). Comparing the activity of CYP 450 in cats and dogs shown that cats have a significant lower activity compared to the dogs (Van Beusekom et al., 2010). Phase two reaction is responsible for making the molecule more water-soluble the facilitate the excretion. This reaction is obtained through conjugation to a glucuronide or sulfate molecule. These reactions occur mostly in the cytosol (Reece et al., 2015). The glucose homeostasis is a complex process that is maintained by different organs such as the pancreatic islet cells, liver and peripheral tissues. Glycogen is the form of glucose that is stored in the muscle and liver cells. It is synthesized when the blood glucose levels are high and serves as a source of glucose for the body when the levels of blood glucose are low. Glycogenesis is the process of glycogen synthesis while glycogenolysis is the process in which the glycogen is transformed into glucose. Abnormalities in these processes can lead to hypoglycaemia, a common sign of severe hepatic disfunction Hypoglycaemia can also be iatrogenic induced by indicating the owners to withdraw water and food before anesthesia for a longer period that necessary in neonatal/juvenile patients. Elevated liver enzymes are the sometimes the first sign of hepatobiliary disease. The typical biochemical panel evaluates the following enzymes: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatise (ALP) and gamma- glutamyl transpeptidase (GGT). Based on their localisation, these enzymes are classified in “hepatocellular leakage enzymes” (ALT and AST) and “cholestatic enzymes” (ALP and GGT). If plasma membrane damages are present due to hepatic inflammation, the enzymes leak into the perisinusoidal space and then into the systemic circulation, causing elevation of ALT and AST. An elevated ALP is one of the most common reported abnormalities in dogs. These enzymes have a high sensibility but a low specificity to hepatic disease. If there is also a concurrent increase of GGT, the changes of an existing hepatic disease or cholestasis increase (Center, 1992; Comazzi, 2004). Changes in this parameters can appear after general anesthesia, but some factors must be taken into consideration: age of the patient, duration and type of the surgery (Turcu et al., 2021). The liver is the place where several coagulation factors, such as fibirnogen, prothormbin, factors V, VII, IX, X, XI, XII and XIII, are synthesized or activated (Weiss et al, 2011). The amount of urea nitrogen in the blood is indicated by the BUN value. The ammonia that results from protein catabolism from the gastrointestinal tract is carried to the hepatocytes through the portal circulation where is metabolized to urea through the urea cycle. Then, the blood urea nitrogen is filtered at the glomerulus and excreted by the kidneys. A decrease in BUN may indicate a hepatic dysfunction or the fact that the blood is shunting the liver. This condition is called portosystemic shunt (PSS). In patients affected by PSS hyperammonaemia occurs. Although there are many toxins involved in the pathogenesis of hepatic encephalopathy (HE), ammonia is the only factor that can be

measures, so the most important. (Ettinger, 2010; Tivers, 2014)

PHARMACOLOGICAL AGENTS USED FOR GENERAL ANESTHESIA

Phenotiazines- Acepromazine is the most widely used phenothiazine agent in veterinary medicine due to its sedative and anxiolytic effects. Note that acepromazine has no analgesic properties and should always be associated with other agents that have these properties. It is metabolised in the liver and excreted in the urine (Clarke et al, 2013). No antagonist is available, as such caution must be taken when using acepromazine in patients with hepatobiliary disease (Johson et al., 2022). One of the major side effects of acepromazine is a dose related fall in the arterial blood pressure due to the vasodilatation. Hypothermia is also a common side effect due to the vasodilatation.

Benzodiazepines are another class of substances that are used in anesthesia. Drugs of this group are used to provide antianxiety action, sedation, *muscle* relaxation, anticonvulsant effects. Benzodiazepines exert their sedative effect by depression of the limbic system and also act at the GABA (gamma-aminobutyric acid) receptors throughout the central nervous system. GABA is an inhibitor neurotransmitter and by acting at this level, benzodiazepines inhibit the transmitter of the neuronal potential (Olkkol et al, 2008). Flumazenil, a competitive antagonist, is available if profound or prolonged sedation is present. Midazolam and diazepam have minimally adverse effects on cardiovascular system and is well tolerated by both healthy and sick animals. However, there are differences between the 2 agents: midazolam is water-soluble and can be administered by intramuscular injection with less local irritation (Jones et al., 1979). One study revealed fulminant hepatic necrosis after oral administration of diazepam in cats. Clinical, the cats presented with lethargy, anorexia and became jaundiced. Biochemical tests showed increased in ALT and AST (Center et al., 1996). The are many pathologies that affect the liver, from mild elevation of the enzymes, to fulminant liver failure. However, many liver conditions require sedation or general anesthesia for surgical interventions. These interventions can vary from liver biopsy to surgical repair of portal venous shunt (Johnson et al., 2022).

The first *α_2 adrenoreceptor agonist* used since 1968 is xylazine, but since then, new potent and highly selective α_2 agonists have been developed. These new molecules are detomidine, medetomidine, dexmedetomidine and romifidine. Most α_2 adrenoreceptor agonists are metabolized by the liver and excreted by the kidneys. The main effects of these substances are sedation and analgesia. The sedation is dose related, but when the sedation reaches the maximum effect, increasing the dose will only increase the duration of the sedation. In combination with an opioid, they produce deep sedation and decrease the dose of inhalant anesthetic. They also produce analgesia through both spinal and central action (Khan et al 1999; Murrell, 2005). The major side effects of the α_2 adrenoreceptor agonists are on the cardiovascular system. In all species they produce profound bradycardia due to the suppression of the cardiac centre and mediated through the vague nerve. However, most studies demonstrated that hepatic blood flow is well-maintained (Johnson et al., 2022).

Opioids are powerful drugs used for pain management. In the central nervous system there are 3 types of receptors: mu, delta and kappa. Based on the affinity of the opioids to those receptors, these can be divided as following:

- Agonist drugs: they have a high affinity to the mu receptors. In this category we can include: morphine, fentanyl, methadone, hydromorphone.
- Partial agonist drugs: they do not have a full affinity to the mu receptors. Here we care include buprenorphine.
- Mixed agonist-antagonist: they act as an agonist to some receptors and as antagonist to other receptors. Butorphanol is the opioid included in this category.
- Antagonist: can reverse the effects of both mu and kappa agonists. Here we can include naloxone (Duke-Novakovski et al, 2016).

The main organ that helps to metabolise the opioids is the liver. After the liver metabolism, the opioids enter the systemic circulation.

The 2 main enzymatic systems that help the opioid metabolism are P450-CYP 450 and UDP (UGT)- glucuronosyltansferases (Mercadante, 2015). Among opioids, remifentanil is a very unique substance. Remifentanil is a potent synthetic mu agonist. Compared to fentanyl, remifentanil is an ultrashort acting opioid, with rapid control of the depth of the anesthesia. It does not accumulate in the body even after a prolong infusion, and has a half-life less than 6 minutes. Considering these properties, it is an excellent choice for total intravenous venous anesthesia (Mercadante, 2015). Like all other opioids, remifentanil shares the same pharmacodynamic properties: dose-related analgesia, central nervous system, respiratory and cardiac depression. Unlike other full mu agonist opioids, remifentanil don not cause histamine release. What makes this opioid special is the ester linkage, making it susceptible to metabolism by hydrolysis by the esterases in the tissues and blood. The pharmacokinetic properties of remifentanil are independent of hepatic and renal function (Stroumpos et al, 2010).

Ketamine is a dissociative anesthetic that produce the dissociative anesthesia. This state is characterized by a dissociation of the thalamocortical and *limbic* system that cause a change of the awareness (Tranquilli et al., 2013). Ketamine is a N-methyl-D-aspartate (NMDA) antagonist, which means that ketamine has analgesic properties. Unlike benzodiazepines, it does not have action on GABA receptors, hence there is no hypnotic effect (Clarke et al, 2013). Hydroxylation and conjugation are the 2 main paths on which ketamine is metabolised. One of the metabolites, norketamine, is also active, this being the reason for the prolong effects (Bettschart-Wolfensberger et al., 1996).

Inhalation agents are widely use in veterinary medicine and very well tolerated by the animals because these substances are removed from the body via lungs. For a safely delivery of the inhalation agent, a special machine is required (Tranquilli et al., 2013). Historically speaking, during the years there were a lot of substances that were used for the purpose anesthesia. In our days, the primarily inhalation agents used in veterinary medicine are isoflurane and sevoflurane. Although the lungs are the main organ on which they act, studies demonstrated that there some degree of hepatotoxicity associated with inhalation agents.

Halothane was the most commonly known anesthetic agent. Developed in 1956, rapidly become one of the most used volatile agents (Safari et al., 2014). In 1969, the National Institutes of Health developed a study on 250 000 cases of halothane administration. This study was designed to examine the possible association of halothane and anesthesia and postoperative massive hepatic necrosis in 34 hospitals throughout a period of 4 years (Moses et al, 1968). There are 2 types of liver reactions associated with halothane administration: the first type 1, mild hepatitis, associated with elevation of liver enzymes (AST and ALT). the values remain elevated for a period of 2 weeks and then resole without treatment (Dabbagh, 2011; Safari et al, 2014). The second form of hepatic injury associated with halothane exposure was severe hepatitis with massive hepatic necrosis. (Safari et al., 2014). The characteristic manifestations of this form are progressive jaundice, hepatic coma and shrinkage of the liver. The etiology of this rare condition has a lot of prone factors, including other drug administration (Trey et al., 1968). After halothane, more modern volatile agents were introduced, including enflurane, isoflurane, desflurane and sevoflurane. A number of studies have demonstrated the effect of inhalant agents on the liver and hepatic function. For example, a case of fulminant hepatic necrosis was observed after inhalator anesthesia with sevoflurane. Right after surgery, no signs were observed, but 20 hours post-operative, the hepatic enzymes were strongly increased and the patient become jaundice. During the next period of time, the patient progressively developed severe hepatic insufficiency, with renal, respiratory and cardiocirculatory failure. Followed all the exams performed post-mortem, the cause of death may be related with sevoflurane exposure (Turillazzi et al., 2007). Although severe hepatic failure was observed after sevoflurane exposure, no apparent renal effects were observed after long duration low flow of sevoflurane or isoflurane (Kharasch et al., 2001). To decrease the minimal alveolar

concentration (MAC) of inhalation agents, different agents were used as bolus or as continuous rate infusion (CRI). One study was conducted to determine how the combination of morphine and cannabidiol (CBD) influence the sevoflurane MAC. The results of the study showed that CBD alone did not reduce MAC sevoflurane and did not enhance the MAC sparring effect associated with morphine used (Orden et al., 2021). A similar study was conducted by Akashi in 2020 on a group of six healthy dogs. The study evaluated the sevoflurane MAC sparring effect after an CRI of dexmedetomidine and/or remifentanil. By administrating this combination, the requirement of sevoflurane administration was significantly reduced (Akashi et al, 2020).

In recent years, there was a growing interest for experimental administrating the halogenated anesthetics intravenously (IV). The major advantage of administrating the volatile agents IV was that the anesthesia was induced faster than administrating through the lungs (Eger et al, 1995). Tests conducted on 15% isoflurane lipid nanoemulsion for general anesthesia showed that there was no evidence of acute renal or hepatic injury. The selected laboratory tests (creatine-kinase, creatinine, BUN and ALT) remained within normal limits 90 minutes after the infusion (Natalini et al., 2017). The goal of another study was to evaluate the renal and hepatic function when 8% sevoflurane lipidic emulsion was administrated intravenously compared to inhaled sevoflurane anesthesia. The following parameters were measured before and after the anesthesia: AST, ALT, lactate dehydrogenase, alkaline phosphatase, total bilirubin and gamma-glutamyl transferase). After all the date were analyzed, the conclusion was that there were no significant differences between the data (Natalini et al., 2016).

CONCLUSIONS

It is very important to create an anesthetic protocol specially designed for the patient. Knowing how each substance can change the liver parameters can help develop a tailored protocol for each patient.

Every substance depends more or less on the hepatic metabolism and the side effect of each substance needs to be well known. Phenothiazines are metabolized in the liver, but because its prolong effects after administration, must be used with caution. Benzodiazepines and opioids rely heavily on liver metabolism. A unique and appropriate opioid that can be used in patients with severe hepatic failure is remifentanil because it is not metabolised by the liver.

α_2 adrenoreceptor agonists do not directly affect the liver, but can cause damage through the cardiovascular effects.

The inhalant agents, isoflurane and sevoflurane, rely on lungs for metabolism and excretion, but some degree of hepatic injury was observed. In case of halothane, the degree of hepatic lesions was far more severe.

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