CONSEQUENCES OF EXPOSURE TO ANESTHETIC FOR THE PATIENT AND SURGICAL TEAM

ABSTRACT

Due to the increasingly interest and care of domestic animal owners to their pets, and to the fact that these animals live longer, anesthesiology is an area which gathers strength today. Therefore, veterinarians and domestic animals are constantly exposed to anesthetics, which are considered exogenous genotoxic agents and have the capacity to change the deoxyribonucleic acid's (DNA) structure and modify its functions. The present review addresses the issues of how intravenous and inhalation anesthetics interfere in the DNA, and discuss the possible consequences of this interference in animal and professional's health. It can be concluded that anesthetic exposure causes DNA alterations not only for the animal being anaesthetized, but also to the surgical crew and to anyone present at surgery. Moreover, we conclude that the safer anesthetic concerning the patient is propofol. The present subject is extensively studied in human medicine, however, its discussion is not unexceptional in veterinary medicine and it must be encouraged, once many of these professionals are also part of a risk group.

Keywords: Anesthesia, Anesthetic gases, DNA damage, Intravenous anesthetics.
Anesthetics are considered exogenous genotoxic agents, which means that they are capable of changing the deoxyribonucleic acid’s (DNA) structure and functions (ALLEVA et al., 2003; SZYFTER et al., 2004). Therefore, both patients and professionals that act in surgical centers are at a risk group due to exposure to these agents. Studies suggest that as higher the exposure to the anesthetics, the greater is the intensity of genetic damage (SARDAS et al., 1998; HOERAUF et al., 1999).

Propofol has been largely utilized for anesthesia induction or continuous infusion, in intravenous general anesthesia. However, several studies have yet to be done about its genotoxic and toxicogenomic effects (KRAUSE et al., 2003; KARAHALIL et al., 2005).

Not all genetic damage is permanent, once there are genes which are responsible for repairing and maintaining genome integrity. These genes act minimizing errors of duplication or anomalous recombination processes, and reducing damages caused by endogenous or exogenous agents (BENHAMOU and SARASIN, 2000).

If repair is not possible, these alterations can interfere in DNA metabolism and at regulatory functions such as cell division and cell cycle regulation (BENHAMOU and SARASIN, 2000). When there is permanent modification in genoma, in a transmissible way, the term mutagenicity is used. Thus, all mutagenic agents are genotoxic, but not always a genotoxic agent is mutagenic (SASAKI et al., 2000).

Inhalation anesthetics are inhaled not only by the patient, but also by the surgical crew, when there is not an efficient drainage system at surgical room. This way, the genotoxicity of these compounds affects a large group of people, when compared to intravenous anesthetics.

**Consequences of inhalation anesthetic exposure to patients and to the surgical crew**

The mechanism through which the inhalation anesthetics induce genetic lesion is not fully known, being only acknowledged that the N2O has direct toxic effects. There is a theory that halogenated drugs with a similar chemical formula to isoflurane can be genotoxic either by reacting directly with the DNA molecule, alkylating the purines’ N7 position, by a toxicity derived from the remaining metabolites of its hepatic/renal metabolism, or yet, from the degradation products in the CO2 absorber (TARDELLI et al., 2013).

Another possibility is the release of reactive oxygen species (ROS), once these compounds can induce several types of lesion in genetic material (ALLEVA et al., 2003; Barbosa et al., 2010).

The increase in lymphocytes’ DNA lesions in patients submitted to invasive surgeries and anesthetized with isoflurane and sevoflurane was also reported by Karabiyik et al. (2001). However, these authors verified a reversible pattern in genetic damage, for both anesthetics, after the third post-operative day.

The study performed by Sardas et al. (1998a) showed the DNA’s repair-genes action. These authors verified that in humans anesthetized with isoflurane there were damage in the lymphocytes’s DNA, however, a regression pattern started 24 hours after the procedure and, from the third day on, the damage levels returned to the basal values. In 5 days, there were no difference between these patients and the control samples, showing the efficiency of repair in this case.

Also in a study with lymphocytes, Delogu et al. (2000) reported high rates of cellular death 24 hours after invasive surgery utilizing isoflurane or nitrous oxide (N2O). In addition, Matsuoka et al. (2001) reported that besides isoflurane, the sevoflurane was also capable of inducing dose-and-time-dependent apoptosis in these cells in vitro.

Corroborating to these studies, Yamada et al. (2002) concluded that the surgical trauma along with the isoflurane anesthesia causes impair immunity by decreasing the number and function of lymphocytes in dogs, highlighting the importance of this issue to anesthesia of small animals.

Barbosa et al. (2010) concluded that using sevoflurane for non-invasive otorhinologic surgery anesthesia, with duration of at least 120 minutes, in ASA 1 patients, was safe to the lymphocytes’ DNA in humans.

Besides the lymphocytes, cells of many organs can suffer with genotoxicity, such as the bone marrow, spleen, brain, lungs and liver cells, when submitted to 1% isoflurane during 30 or 60 minutes (KIM, 2006).

Eger et al. (1997) have studied compound A genotoxicity, which is a component generated by the reaction of sevoflurane with the CO2 absorbed in the presence of heat. They have reported that ovarian cells of Chinese hamster exposed to...
compound A concentrations similar to the ones obtained in low flow of sevoflurane, feature an increase at sister chromatids exchanges frequency in the same chromosome. This is one of the few studies relating genotoxicity to the compound A in a mammalian cell model (KARABIYIK et al., 2001).

Another anesthetic still used in veterinary medicine, especially in large animals is halothane. It has been suggested that the mechanism through which this drug act in the cells is changing the ions cytosolic levels and inducing damage to the cell membrane, causing cell damage (genotoxicity) or apoptosis (cytotoxicity) (JALOSZYNSKI et al., 1999). Halothane's cytotoxic effect could be not observed, when compared to other halogenated agents, because the damaged genetic material of these dead cells is collected along with the DNA from the cells which suffered genotoxic action, generating false positives in the comet assay (JALOSZYNSKI et al., 1999).

In a study conducted by Kvolik et al. (2005), tumor cells were exposed to halogenated agents, and apoptosis and a greater antiproliferative effect were observed in the group exposed to halothane, in comparison with groups exposed to isoflurane and sevoflurane. These authors suggest that the bigger metabolization required by this anesthetic along with the bromine incorporated in the molecular structure are responsible for these results.

The National Institute for Occupational Safety and Health (NIOSH) established, in 1977, the safe gas concentration limits in the surgical environment. The halogenated agents were all included at the same category, and must not exceed 2ppm at the surgery room. On the other hand, nitrous oxide (N2O) was considered in a separate category, and the concentrations accepted for it were until 25ppm during the anesthesia (WIESNER et al., 2001).

The safety of these levels were proven in a study conducted by Wiesner et al. (2001), who compared the incidence of genetic damage between physicians from a hospital, who were exposed to high levels of anesthetic in the environment, and professionals exposed to levels within the limits established by NIOSH. It is worth to point out that the free gas concentration admeasurement can be performed in an efficient and quick way with chromatography or mass spectrophotometry.

Professionals who work at surgical centers are exposed to lower anesthetic concentrations than the patients, however, this exposure generally extends for years. The surgical crew oftenly presents headaches, malaise and even more serious complications, like carcinogenicity, mutagenicity, teratogenicity, fertility reduction, problems during pregnancy and increase in the rates of miscarriage (BILBAN et al. 2005; CHANDRASEKHAR, 2006). These effects are directly related to the anesthetic gas type, exposure time and environmental concentration of it (BAYSAL et al. 2008).

Studies carried out with anesthesiologists show that these professionals have more chromosomal alterations than professionals who are not exposed to these anesthetic gases (LEWINSKA et al.; 2005; ROZGAJ et al., 2009; MUSAK et al. 2013). Wronska-nofer et al. (2009) evaluated professionals who were exposed to N2O and halogenated compounds for at least 5 years and verified a positive correlation between genetic damage intensity and free N2O concentration in the environment.

Miscarriage seems to be the most common consequence for the chronic exposition to inhalation anesthetics, affecting not only the exposed professionals (GAUGER et al., 2003) but also their wives (GUIRGUIS et al., 1990). The N2O also brings reproductive consequences, as observed in the assistants of dentists, who had fertility reduction and increase in miscarriage frequency after continuous exposure to this gas (ROWLAND et al., 1995).

Pregnant women exposed to this gas may also present preterm labor, congenital anomalies (as cardiac, respiratory, neurological, epithelialization failures and others), low weight and smaller size of the baby at birth (GAUGER et al., 2003).

Male professionals are also jeopardized. Studies showed that halothane is capable of altering the sperm motility more than other halogenated compounds (KAYMAK et al., 2012), besides altering male sexual behavior, which was well seen in rats, based on their lower interest on the female, higher number of mounting attempts and extended time until ejaculation (OROPEZA-HERNANDEZ et al., 2002).

Besides reproductive issues, Lucchini et al. 1996 compared the neurobehavioral performance of anesthetists practicing intravenous anesthesia or inhalation anesthesia during one week and verified that the halogenated compounds along with the N2O are capable of jeopardizing these professionals performance.

Despite the development of drainage systems, the pollution level in the surgery room depends on multiple factors like the circuit utilized (closed/open) and the anesthetic technique, as for example the utilization of high or low oxygen
flow, use of facial mask or utilization of a cuff in the orotracheal tube

In most veterinary clinics and hospitals, there is not a suitable cleaning and removal system for the anesthetic gases, and therefore, it is suggested that veterinary anesthetists are exposed to higher concentrations of anesthetic gases than those reported in human hospitals.

Consequences of the intravenous anesthetic exposure to the patients.

Propofol, which is a general intravenous anesthetic widespread use in veterinary medicine, presents a phenolic group in its chemical structure similar to the butylated hydroxytoluene and to the α-tocopherol (vitamin E), which are powerful antioxidant agents (TSUCHIYA et al., 2002). Aarts et al. (1995) reported that propofol is capable of inhibiting plasma lipid peroxidation in the concentrations usually utilized in anesthetic practice. However, it is also reported that the antioxidant effect occurs only when high concentrations of this agent are applied (GREEN et al., 1994).

This drug's capacity to attenuate the lipid peroxidation by being an antioxidant agent is extremely positive for the patient due to the fact that during surgery occurs oxidative stress intensification by production of ROS, with a consequent weakening of the organism's biological defenses when trying to fight it. Therefore, the utilization of drugs with antioxidant activity during trans-operative is a possibility to combat this immune depression in the patient (KANG et al., 1998).

Inhibition of lipid peroxidation causes blockage of the malondialdehyde formation (MDA) and this way, this anesthetic can protect blood and another tissues from the ROS action (SAYN et al., 2002).

Regarding genotoxic potential of propofol and its metabolites, negative results were observed in vitro in mutagenicity tests in bacteria (Salmonella typhimurium), fungi (Saccharomyces cerevisiae) (Trapani et al., 2000) and in mammalian cell culture (CHO) (TOMIOKA et al., 2000). These results agree with in vivo results performed in humans under this type of intravenous anesthesia (KRAUSE et al., 2003; KARAHALIL et al., 2005; BRAZ et al., 2009).

Acquaviva et al. (2004) reported that propofol presented anti-apoptotic effect, reduced the citotoxicity and prevented DNA damage in astrocyte culture, which are relevant aspects to the neuroprotection during anesthesia. However, other authors state that high doses or exposition to propofol for extended time can cause apoptosis of neuronal cells in the developing brain and, therefore, its usage in pediatric anesthesia must be cautious (FREDRIKSSON et al., 2007; CATTANO et al., 2008; BERCKER et al., 2009; ZOU et al., 2013).

Fredriksson et al. (2007) reported that a high dose, of 60mg/kg, of this agent in 10 years old mice triggered apoptosis of neuronal cells, corroborating with Cattano et al. (2008). Zou et al. (2013), showed that the exposition of rat's embryo stem cells to propofol leaded cells to apoptosis.

Delogu et al. (2001), in an experiment with human lymphocytes, didn't find cell death by apoptosis in vivo, with use of clinically utilized concentrations of propofol. These authors suggest that the antioxidant properties of this drug can, in some way, inhibit the way through which mitochondrial free radicals interfere with apoptosis.

Regarding this drug interference in the reproductive system, there are evidences that, in rats, it acts negatively in the oocyte capacity to fuse with the spermatozoid and causes adverse effects to the embryo during its development to the stage of blastocysts (TATONE et al., 1998).

Tomioka and Nakajo (2000) found no increase in the frequency of chromatid sister exchanges in chinese hamster ovarian cells in vitro. In neonatal cell culture, propofol induced lesions in GABAergic neurons and glial cells (HONEGGER and MATTHIEU, 1996).

However, Braz et al. (2009) performed a study in ASA1 human patients submitted to elective surgeries of less than 90 minutes, with propofol as the anesthetic and concluded that there is no genetic damage under these circumstances. Karahalil et al. (2005) also found no genetic lesion at blood cells of patients in cardiac surgeries, with the use of propofol. It is worth to point out that these authors also compared propofol action along with diazepam or fentanyl and in none of these cases there were DNA damages.

The intravenous anesthesia was studied in pediatric patients by Krause et al. (2003) during minimum invasive surgeries and similarly to results found in adults, propofol did not cause genetic damage.

As far as we know, literature doesn't provide information about genotoxicity to canines or felines undergoing inhalation or intravenous anesthesia, suggesting the elaboration of
It is important to highlight that performed studies with propofol genotoxicity involve, in general, patients under anesthesia or cells/tissues exposed to the anesthetics for a short time. Therefore, the need of more studies is reiterated, especially in veterinary medicine, in order to establish safer doses and exposition time limits for these drugs usage in our patients, once some of them are submitted to long anesthetic periods and sometimes has to undergo many surgical procedures during life.

In the literature at our reach there are no studies relating genotoxicity and the use of barbiturates and etomidate, which are intravenous anesthetics also utilized in the anesthetic routine.

FINAL CONSIDERATIONS

According to presented facts, it is possible to observe that the exposition to anesthetics is a risk not only to the patients, but also to the surgical crew. This subject is extensively studied in human medicine, however, its discussion is not unexceptional in veterinary medicine and it must be encouraged, once many of these professionals are part of a risk group.

We also highlight the importance of studies about the consequences of anesthetics to the organism of patients exposed for long periods or submitted to many surgical procedures.

REFERENCES


