ABSTRACT

To induce the anesthesia, specially injectable general anesthesia, it supposes the use of an increased number of substances, that usually overcome 4 to 8 number, and which may reach in certain situations, in human medicine, to 15 – 20 (in major complicated surgical interventions).

To this therapeutically fact it may be added the following:

- in the case of association of more than two substances is practically impossible to prevent the effects and to mark down the consequences;
- the side effects are direct proportionally to the number of drugs administrated to a patient and with their lasting effect.

The number of the administrated drugs, together with lack of knowledge (real or just lack of information) of the action mechanism and interaction of the anesthetic drugs, changes sometimes the anesthesiologist into a helpless spectator to a drama that he triggered and whose evolution got out of control.

The research thesis with the title: *Assessment of some injectable medicaments agents inductors of the general anesthesia on hemodynamic and acid-base balance functions in dog*, is containing a number of 229 pages and is structured in conformity with actual legal regulations in two main parts: first part - *Actual stage of knowledge,* that contains a number of 64 pages, representing 31 % and second part – *Personal researches,* that contains a number of 140 pages, representing 69 % of the volume of the thesis.

In the first part, structured in 5 chapters, are presented, in succinct manner, the data from scientific literature referring to the subject of the thesis and that were used in second part of the thesis as reference data for the interpretation and discussions of the obtained results. In ***the first chapter,*** entitled *The influence of the anesthetic substances on main pharmacokinetic and pharmacodynamic parameters,* are suggestively presented data that indicate the pharmacologic profile of the anesthetic substances and the fact that their bioavailability at the level of the receptor site from the target tissues will depend on the dynamic of the pharmacokinetic process. This process may differ related to physiologic and pharmacologic modifications due to anesthesia and features of the species. The interpretation of the data will be made taking into account the influences of the anesthesia on pharmacokinetics and biologic bioavailability of the studied drug. These observations allow the best choice for the anesthetic technique.

The second chapter is referring to *The impact of anesthesia on the main functions of the animal organism* and presents pieces of information related to the modifications of the cardiovascular response during anesthesia, the variations of the blood pressure, of the breathing rate and digestive tract motility, renal function and neuromuscular junction.

In the following ***two chapters (three and four)*** of the first part, with the titles *The neurochemistry of pain sensation* and respectively *The concepts of pain management and pain control,* are described neuroactive substances, amino acids, the amines and peptides involved in pain control and modulation. The lesions produced to the tissues, leads to local biochemical modifications and vegetative reflex reactions, meant to assure protection. The local biochemical modifications are produced by the release of the intracellular substances from the damaged tissue into extracellular fluid; these induce local pain, sensibility and hyperalgia. These substances are the ions of H^+ and K^+, serotonin, histamine, prostaglandins, bradikinin, SP and others. Bradikinin, acetylcholine and K^+ activates directly the nociceptors, and the others, especially prostaglandins, sensitizes the nociceptors facilitating depolarization. The P substance increases the extravasations and inflammation. The activation of the peripheral nociceptors generates impulses that, after reaching to the dorsal spinal horn, have peripheral descendent modifications, locally to segment and beyond segment. The sent impulses produce segment nocifensive vegetative reflex reactions, somatomotor and sympathetic. The ascendant afferent impulses are transmitted in different parts of the cerebral trunk and brain. The impulses that reach to the cerebral trunk initiate beyond segment reflex reactions and activate the modulation descendent system; the impulses that reach to the cortex induce cortical reactions. A great number of substances are included as hypnotic, sedative and tranquillizers. In reality, these types of effects are very hard delimitated, depending on dose and most of the time they intricate. Thus, small doses of hypnotic induce sedation; sedatives treat sometimes anxiety, the tranquillizers may determine decrease of performances and induces sleep. Pain control may be performed with general anesthesia techniques and methods (narcosis), by general analgesia with morphinic substances, general analgesia with benzodiazepines and narcoleptic substances, neuroleptanalgesia and narco-neuroleptanalgesia, by dissociative anesthesia or „Somatic – Analgesia and by local and regional anesthesia.

The hypnotic substances, barbituric like or benzodiazepines, increase the sleep process, increase total sleep duration and decrease the nocturnal frequency and duration of awaking. Often, is subjectively described a sensation of resting and refreshing sleep. Hypnotic substances modify the stages of the physiologic sleep, as they are defined by the electroencephalographic activity, the presence or absence of the ocular movements and dreams, the evolution of different

physiologic index – movements and muscular tonus, pulmonary and heart frequency, the pupil dimensions.

The last ***chapter (V)*** of the first part, with the title *Screening of the general anesthesia,* contains aspects related to the elaboration of a screening strategy of the anesthetized patient and of the profoundness of anesthesia. The screening gives data that improve the safety of anesthesia and at the same time offers possibilities to evaluate the functions of the organism. A minimum screening (standard) was initiated by the Harvard medical school and then by the American society of anesthesiologists in 1986. Similar standards were adopted by other anesthesia societies, becoming compulsory for all anesthesiologists belonging to the society. In veterinary medicine is necessary the anamnesis, registration of the anesthetic drugs and of the used procedures, as part of the surgical act. Geriatric animals or with potential risks, represent a concern apart, and registration of the successful anesthetic episodes (extra care) are very important for the veterinary doctor, who may have the chance to perform anesthesia in such an animal for the first time.

Second part, with researches, is structured in 8 chapters and contains the aim and the orientation of the researches, studied material and used methods, obtained results and their interpretation, general conclusions closing this part.

Chapter VI, *Aims, anesthetic protocol, material and method,* underline the motivation of this research, describing the main objectives of the thesis. The hypothesis of this subject left from the necessity to adopt and implement a correct screening strategy, made through analysis and interpretation of the hemodynamic function and acid-base balance modifications of the anesthetized patient (dog), on injectable route, using different anesthetic protocols, which include a wide variety of chemical compounds, especially propofol. The main objectives followed during research were:

- establishing the immobilization techniques – anesthetic balanced – through elaboration of some combinations (associations) of analgesic substances together with propofol, which to present : reduced toxicity, minimal interference with vital functions of the organism, minimal metabolic function, rapid and complete metabolic recovery;
- screening of the respiratory and cardiovascular functions;
- screening of the effects of these anesthetic associations on main indicators of the acid-base balance.
- Quality and quantity evaluation of the analgesic activity of these associations (by establishing the intensity and duration of the antinociceptive response), in correlation with the modifications of the hemodynamic parameters and acid-base balance.

Chapters VII – XI, contain the results of the researches regarding the intravenous administration (bolus or continuous perfusion) of propofol, alone or in association with other anesthetic agents, respectively medetomidine, chlorpromazine, xylazine, butorphanol and buprenorphine in dog. Was proved that respiratory apnea and depression are the main important side effects of the propofol over dosage, reactions that may be correlated to significant modifications of O_2P and CO_2P and hemodynamic balance, at different moments of the anesthesia. In case of major surgical act, very painful, following to perform a special antinociceptive protection with a minimum risk on the important functions of the organism, the results obtained underline the superior quality of some anesthetic protocols with propofol in association with adrenoreceptor alpha$_2$-agonists (medetomidine) and opioids (butorphanol, buprenorphine). These determine a rapid induction of the anesthesia, a longer duration of the surgical act and a rapid recovery period without being followed by special side effects, aspects that have a benefic effect on hemodynamic balance of the organism. The analgesic effect is manifested on a period of time from 6 to 8 hours, aspect influenced by the dosage level, miorelaxation degree and body temperature.

Chapter XII, *Observations and recommendations regarding the pharmacology of propofol in dog*, contains aspects related to the physical-chemical, pharmacokinetic and pharmacodynamics proprieties of this anesthetic substance. Also to be mentioned, the fact that this anesthetic agent, less soluble in water, is not part of the known anesthetic classes, being considered a non-dissociative non barbituric intravenous anesthetic agent, in which, the main solvent (polyoxyethylene resin oil - Cremofor EL) determined numerous anaphylactic reactions. In the new formulation, it is presented as an oily – milky emulsion, white color, insoluble in water, of 1% concentration. The propofol has a rapid distribution ($t_{1/2}\alpha$ = 2 - 10 minutes) in highly vascularized tissues such as brain and visceral tissues. Thus, it determines a rapid loss of consciousness, in 40 ± 1,5 seconds, without excitation phase („subcortical rebellion") or hypersalivation. An aspect, confirmed both by our studies in dog, is referring to different debut of the anesthesia depending on the used technique: continuous perfusion and i.v. bolus, being between 1,2 ± 0,2, respectively 1,4 ± 0,2, depending on the used dose. The propofol allows a good quality induction. The relaxation of the skeletal muscles is great and the tonus of the masseter muscles is sufficiently depressed in order to allow the anesthetist to perform different preanesthetic maneuvers (examination of the oral cavity, intubation), moreover that the laryngeal and pharyngeal reflexes are very diminished. The duration of the surgical anesthesia obtained after a single dose of propofol in dogs preanesthetized with chlorpromazine and medetomidine had a mean between 12,3 ± 1,89 and 25,2 ± 1,78 minutes, the fast and integral recovery being due to rapid redistribution. Total recovery from anesthesia with this agent is prolonged in the

case of continuous intravenous perfusion or multiple readministration (i.v. bolus) and all together, the propofol presents modest cumulative proprieties than barbituric substances; recovery from propofol being more rapid than from tiopenthal. This is one of the main advantages of this anesthetic agent. Propofol influences at the same time the cardiac and vasomotor functions. Indeed, it may be noticed a reduction of the cardiac inotropism with vasodilatation. This fact determines a decrease of the arterial pressure (arterial hypotension) from 15 to 40%, for short period of time, due to rapid elimination of the product. It is compensated in the majority of the cases with a sympathetic activation that leads to an increase in cardiac frequency. Yet, in some situations, the reduction of the sympathetic tonus is greater than the reduction of the parasympathetic tonus and then it may be noticed bradycardia in induction of the anesthesia that increases hypotension. In order to maintain to normal the cardiac debit and arterial pressure, the animal is preferred to be sufficiently hydrated with electrolytic solutions, before the induction. Thus, the hypotension induced by propofol is limited, although its negative inotrope action is not obvious. The depression of the CNS is dependent to the administered dose. The propofol increases the GABA-ergic transmission. It „antagonizes" the effects of glycine and interacts with dopaminergic system and sodium channels of the CNS. This explains, together with diminishing of the cerebral activity, its anticonvulsive action.

In the conditions of a corresponding dosage and balanced combinations, wishing only to correct the negative effects of the associated substances, the modifications of the hemodynamic function and acid-base balance are minimal without being clinically significant.