Do we really know the pharmacodynamics of anaesthetics used in newborns, infants and children? A review of the experimental and clinical data on neurodegeneration

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Abstract

The practices of anaesthesiology and intensive therapy are difficult to imagine without sedation or general anaesthesia, regardless of whether the patient is a newborn, baby, child or adult. The relevant concerns for children are distinct from those for adults, primarily due to the effects of anatomical, physiological and pharmacokinetic-pharmacodynamic (PK/PD) differences, which become increasingly important in the brains of children as they develop. The process of central nervous system maturation in humans lasts for years, but its greatest activity (myelination and synaptogenesis) occurs during the fetal period and the first two years of life. Many experimental studies have demonstrated that exposure to anaesthetic drugs during this period can induce neurodegenerative changes in the central nervous systems of animals. The extrapolation of these results directly to humans must be performed with great caution, but anaesthesiologists around the world must begin to debate the safety of general anaesthesia in humans. Prospective trials should continue being carried out, and anaesthesia and surgery, delayed if possible among the smallest patients. The simultaneous use of different anaesthetics with the same potential neurotoxicities should also be avoided, potentially in favour of regional anaesthesia techniques, in this group of patients.

Key words: nervous system, central, sleep; nervous system, anaesthesia, neurodegeneration

Sleep is one of the most mysterious riddles facing anaesthesiologists, psychologists, neuropsychologists and psychiatrists. An essential question posed by many scientists is, what does the brain do during sleep? Is natural sleep similar to that induced by drugs [1]? Does pharmacological sleep differ in a newborn or infant compared to a child or adult? Can this type of sleep affect the further psychological-emotional development, cognitive functions and ability of a child to learn [2]?

It is difficult to imagine modern anaesthesiology and intensive therapy without sedation or general anaesthesia, regardless of whether the patient is a newborn, infant, child or adult. However, the population of paediatric patients differs markedly from that of adults, potentially demanding different and individual approaches for each affected child. The anaesthesiological dissimilarities are mainly anatomical, physiological and pharmacokinetic-pharmacodynamic and grow particularly relevant during rapid brain development.

The aim of the present paper is to review the literature regarding the basis for natural and anaesthetic sleep, as well as the neurodegenerative effects of drugs used for the sedation and general anaesthesia of the brains on newborns, infants and small children.
MATURATION OF THE CHILD’S CENTRAL NERVOUS SYSTEM (CNS)

The brain starts to develop already during the first days of foetal life when the neural plate originates from ectoderm, underlying the development of the neural tube. In mammals, the brain takes shape between the 4th and 6th week of foetal life. At week 7, the configuration of a child’s brain is similar to that of an adult. The brain sends impulses, which coordinate the functions of some organs, and the first synapses are formed in the brain [3].

The maturation of the CNS in humans lasts many years, although the greatest activity is observed during the foetal stage and the first two years of life. The essential elements of CNS maturation, also from the anaesthesiological point of view, are myelination and synaptogenesis [4]. By the end of the second trimester of foetal life, the brain contains its complete number of neurons, i.e., 100–160 billion, among the 300–500 billion in the entire nervous system. Beginning in the 5th month of foetal life, the myelination of the nerve fibres begins, thanks to oligodendrocytes. Before birth, however, only the fibres passing through the hypothalamus and subcortical nuclei are myelinated. Further myelination occurs during the first years of life, successively implicating the pyramidal pathways and the reticular system until finally the associative fibres of the cerebral cortex are myelinated around 20 years of age.

The first synapses have already been formed by the end of the 2nd month of foetal life; however, their number and activity substantially increase during the neonatal period, infancy and the first two years of life, which are associated with dynamic development and new skills acquired by a small child. The final number of interneuronal connections made is estimated at 100 trillion.

The development and maturation of the nervous system continues for many years after birth. The control of the emotional-mental life of a newborn is taken gradually over the upper regions of the brain, which include the cerebellum and basal ganglia’s control over movements; the limbic system’s responsibility for emotions and memory; and the supervision of the cerebral cortex, the centre of all spontaneous behaviours, over conscious experiences and rational abilities. At birth, the cortex is the least-formed part of the brain.

 Appropriately formed neurons and synapses are particularly relevant for infants and small children during the development of their memories and abilities to learn. Memory is formed thanks to extreme plasticity of the nervous system and involves the structural transformations of interneuronal connections. The brain has more than one region responsible for memory, but still, the hippocampus is considered the essential site of memory enhancement, a specific link between the past and the present. Another key feature of the brain is its state of consciousness, which is usually equated with a state of mind [5]. Self-consciousness pertains mainly to humans, but most likely also to dolphins, elephants and chimpanzees and is thus likely to be associated with the right hemisphere, more specifically with the callosal gyrus and prefrontal cortex. Damage to or dysfunction within these brain structures in the early period of life, which may, for example, be induced by some drugs, including anaesthetics, can lead to the development of emotional and cognitive disorders and an impaired ability to learn. It is therefore essential for modern anaesthesiologists, particularly those responsible for paediatric anaesthesia, to assess the effects of the drugs used during anaesthesia or sedation on the developing brain.

SLEEP MECHANISMS

The major physiological role of sleep is to restore CNS balance or, using the language of informatics, to reset the computer, i.e., the brain.

The states of sleep and wakefulness are primarily regulated by the hypothalamus and two nuclei located within it [6]. The ventrolateral preoptic nucleus (VLPO) is responsible for the induction of sleep, whereas the tuberomammillary nucleus (TMN) activates the state of wakefulness. An essential role in activation of the switch on/off cycle is played by two neurotransmitters: γ-aminobutyric acid (GABA) from VLPO and histamine (HA) associated with activation of TMN, which is its only source in the CNS [7]. During sleep, the VLPO neurons are activated and stimulate the release of GABA to TMN, blocking the neurons of this centre and inducing sleep with the maximum activity during rapid eye movement (REM) and non-rapid eye movement (NREM) phases. The indirect marker of neuronal activity in the above and other centres of the nervous system is the cellular proto-oncogene c-Fos, the expression of which increases with the appearance of functional potential in the nerve cells [8]. The VLPO neurones are implicated as the places in which the action of the majority of anaesthetics is mediated.

Another centre involved in the regulation of sleep/wakefulness states includes lateral hypothalamus (LAT) neurones releasing orexin A and B (previously known as hypocretin 1 and 2), the action of which is additionally strongly correlated with the tone of skeletal muscles [9]. During deep sleep, the activity of the above neurons gradually decreases, which is confirmed by decreased c-Fos activity in this region and only sporadic increases during the REM phase. A similar clinical effect is induced by sevoflurane and isoflurane, the action of which can temporarily abolish the release of endogenous orexin. The above mechanism is highly likely to explain rapid increases in muscle tone and development of seizures, especially in children anaesthetized with high concentrations of sevoflurane [10]. The locus coeruleus (LC), located in the pons, is the largest source of noradrenaline.
(NA) in CNS. The highest activity of neurones of this region is observed during wakefulness and activity but decreases in the NREM phase and further deepens during the REM phase. Dexmedetomidine, an agonist of α₂ receptor, which can be administered directly to LC induces the hypnotic effect similar to that of VLPO, is also expressed in decreased amounts of c-Fos, as opposed to ketamine [11, 12]. The next neurones of the laterodorsal tegmental (LDT) nucleus and pedunculopontine (PPT) nucleus contain cholinergic fibres reaching various brain regions, including the thalamus, hypothalamus, black matter, cerebral cortex and reticular system. They secrete acetylcholine (Ach) at the nerve ends, both during the physical activity and REM phase. The use of isoflurane and ketamine, as well as other neurotransmitters, is associated with increased amounts of GABA and reduced amounts of Ach in the reticular system [13, 14].

As far as regulation of circadian rhythms is concerned, the main role is played by over 20 thousand melatonin-sensitive neurones of the suprachiasmatic nucleus (SCN). They receive information directly from the retina and transmit it further to the hypothalamus and pituitary, regulating the release of melatonin and serotonin and modulating the body temperature during sleep [15]. In humans, the endogenous cycle of SCN activity is mediated by GABA-ergic systems and lasts 24 h 11 min, on average, preserving its cyclic rhythm even during long-term lack of light. Interestingly, neurons of this region are capable of expressing genes induced by the stimulating factor, i.e., a light stimulus [16].

Still another active place in the brain responsible for modulation of sleep is the suture nucleus located in the brain stem as a characteristic thin line, the nerve fibres of which reach the higher CNS regions, i.e., the thalamus, hypothalamus, limbic system and cerebellum, as well as posterior spinal horns, located inferiorly, modulating the processes of pain conduction. The active substance responsible for the induction of physiological sleep, as secreted at the nerve ends, is serotonin [17]. Experimental studies have demonstrated that drugs blocking serotonin receptors induced even several-day lacks of sleep. It is worth noting that the production of serotonin at birth is markedly lower than that in an adult, slowly increasing until the 12th month of life. The above explains the higher pain sensitivities of new-borns and infants whose endogenous mechanisms, responsible for limiting pain stimulus inflow to the supraspinal centres related to pain perception, are distinctly impaired [18].

MECHANISMS OF HYPNOTIC ACTION

General anaesthesia consists of a triad involving deep sleep (loss of consciousness), analgesia and muscle relaxation. From the pharmacodynamic point of view, the mechanism of reversible loss of consciousness is very difficult to explain. Studies on the mechanisms of sleep induced by hypnotics have been carried out for several decades, but the mechanisms in question are still not fully understood [19, 20]. The key assumption of general anaesthesia or sedation is its complete reversibility, meaning that the use of drugs does not exert permanent effects on the human brain and spinal cord. Unfortunately, this assumption was recently revised when animal studies demonstrated a directly injurious impact of these drugs on the immature CNS.

Theories explaining the mechanisms of action of sedatives and hypnotics have changed repeatedly. The first theory, based on non-specific physicochemical phenomena, was not confirmed and was quickly rejected. At the turn of the 19th and 20th century, two researchers, Meyer and Overton, independently described the linear relation between the force of action of an anaesthetic and its solubility in lipids [21, 22]. Their theory was based on observing the phenomenon in olive oil. The relation was so strong that it suggested a non-specific action of anaesthetics that was solely dependent on their solubility in lipids; the place of action was considered the high-lipophilic cell membranes in the nervous system. It was impossible, however, to explain the actions of all agents, including ketamine, in this way.

The above considerations formed the basis of another theory (called the lipid theory), according to which lipophilic compounds are able to permeate the bi-layered cell membrane, changing the configuration of its phospholipids and making its structure fluid, thereby increasing its volume [23]. The argument against the above theory was based on the fact that an increase in temperature of 1°C caused a similar thickening of cell membranes and simultaneously abolished the action of anaesthetics. The updated lipid theory assumed that the anaesthetic changed the pressures in the bi-layered cell membrane, altering the conformation of membranous ion channels to generate in a certain anaesthetic effect [24].

According to the most recent theory of ion channels, the action of anaesthetics involves the modification of neurotransmitter ligands with membranous receptors, leading to the opening of ion channels by either changing the membranous potential or direct binding to the ligand [25]. In anaesthesiological practice, the vital ligand receptors are divided into the following: pentameric receptors — nicotinic and acetylcholinergic (muscle relaxants), serotonin 5-HT₁ receptors (propofol, ondansetron), ionotropic purinergic receptors (pentobarbital), G protein-coupled receptors (GPCRs) for all adrenergic, muscarinic, cholinergic and opioid receptors, glycine receptors (inhalational anaesthetics), γ-aminobutyric type A (GABAₐ) receptors (the majority of known anaesthetics), ionotropic glutamnergic N-methyl-D-aspartate (NMDA) receptors, α-amino-3-hydroxy-5-methyl-4-izoxazolopropionine (AMPA) and cainian receptors (nitrous oxide, xenon, ketamine).
Table 1. Selected general anaesthetics and their effects on GABA and NMDA receptors

<table>
<thead>
<tr>
<th>Agent</th>
<th>GABA agonist</th>
<th>NMDA antagonist</th>
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<tbody>
<tr>
<td>Sevoflurane</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Desflurane</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Propofol</td>
<td>+</td>
<td></td>
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<tr>
<td>Thiopental</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Etomidate</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>+</td>
<td></td>
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<tr>
<td>Chloral hydrate</td>
<td>+</td>
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<tr>
<td>Fentanyl</td>
<td>+/-</td>
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<tr>
<td>Morphine</td>
<td>+</td>
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<tr>
<td>Methadone</td>
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GABA — gamma amino benzoic acid; NMDA — N-methyl-D-aspartic acid

MECHANISMS OF THE NEUROTOXICITY OF ANAESTHETICS

GABA, and NMDA play a significant role in anaesthesiological practice (Table 1). The GABA receptor is located in the postsynaptic membrane of grey matter neurons, mainly in the cerebral cortex, cerebellum, thalamus, hypothalamus and limbic system. Although the clinical effect of the stimulation of the GABA receptor is the inhibition of cerebral functions, the receptor is not actually an inhibitory one. Its endogenous ligand, γ-aminobutyric acid, is the stimulating neurotransmitter in the immature brains of new-borns, as opposed to adults; this fact can be used to explain the phenomenon of midazolam-induced seizures in new-borns, particularly preterm ones [26, 27]. The receptor is composed of several subunits: α, β, and γ. The binding site of γ-aminobutyric acid is between α and β, while that of benzodiazepines falls between α and γ. Some of these receptors are activated by alcohol, steroids or barbiturates. The effect of the ligand-receptor reaction is the opening of chloride channels and hyperpolarisation of the nervous membrane, leading to the clinical effects of anaesthesia, amnesia and anxiolysis. Barbiturates prolong the time of ion channel opening (initiated earlier by benzodiazepines) via synergism [28].

The NMDA receptor is localised postsynaptically in the stimulating dendrites of the hippocampus, cerebral cortex and spinal cord, as well as presynaptically, in the axons. Ethanol and dizocilpine number among its antagonists; the latter has been used mainly in experimental studies to demonstrate the damaged structure of the nervous cell after its application [29].

In summary, the mechanisms of action of the drugs used during sedation or general anaesthesia involves the enhancement of neurotransmission inhibition by agonist effects on γ-aminobutyric acid or the inhibition of glutamate effects on the NMDA receptor. The damage to neurons can be, and most likely is, caused by the action of agents used during general anaesthesia via GABA and NMDA receptors, which are found on the site of action of the majority of drugs applied during anaesthesia. Thus, the pharmacological effects include not only the desirable effect of the form of unconsciousness but also the unfavourable neurodegenerative impacts that lead to apoptosis, DNA defragmentation and death of CNS cells [30]. The complex process of apoptosis is initiated by, among others, Bax (Bcl2-L-4), which leads to mitochondrial membrane dis-integrity followed by the extensive activation of caspases. Moreover, the cytoskeleton of the nervous system is also disintegrated, losing its contact with the basilar membrane. The remaining cell organelles are intact and, in this form, are removed from the dead cell. If this process affects nerve cells during their intensive synaptogenesis (between the 27th week after conception and 3rd year of life), severe consequences, such as irreversible damage to and dysfunction of the brain, can result.

The neurodegenerative effects of the agents used during general anaesthesia have been analysed and confirmed in many experimental studies in animals during the period of the active maturation of their CNS. The majority of the data available has come from the above studies. An important task facing anaesthesiologists is how to determine whether these phenomena also arise in humans undergoing general anaesthesia, and if so, whether it can be prevented.

EXPERIMENTAL STUDIES

Studies carried out in rodents and primates during intensive synaptogenesis have demonstrated the direct injurious effects of anaesthetics on extensive regions of the brain, despite maintained homeostasis during exposure to the drugs and the elimination of other harmful factors, such as hypoxia and ischaemia. Rodents, more precisely rats, are born with the brain at an earlier stage of development than humans. The rapid development of their brains takes place during the first week of life, which corresponds to the development of human brains during the third trimester of pregnancy and the first 24 months of life. Because agonists of the GABA receptor and antagonists of the NMDA receptor damaged rat brains in this period, it was assumed that the same neurodegenerative effect is likely to occur in humans in the corresponding stage of development of their brains. In Macacus rhesus, the respective relationships affect the final two months of pregnancy and the first two months of life (Fig. 1).

A breakthrough in studies on the neurotoxicity of anaesthetics was the work of Ikonomidou and colleagues [31], who analysed the effect of dizocilpine, a potent antagonist
of the NMDA receptor, and confirmed the neurodegenerative influence of this agent on the cerebral cortex at levels 3–39 times stronger than found in controls. Similar results were obtained for other NMDA antagonists, i.e., phencyclidine and ketamine, and confirmed earlier findings. Another relevant study showed that 6-hour anaesthesia with midazolam, nitrous oxide and isoflurane had degenerative effects on rat brains, depending on types of drug, amounts of drugs used simultaneously, exposure times and doses [32]. The degree of apoptosis was assessed using immunocytochemical and histochemical methods in selected portions of the brain; additionally, the activity of caspases was evaluated. The findings did not confirm this type of damage to the cells when only one agent was used, irrespective of whether it was midazolam or nitrous oxide; otherwise, when isoflurane was administered, the degree of apoptosis was concentration-dependent. The use of two or three agents simultaneously always led to dramatic apoptosis in the cortex, thalamus and hippocampus, resulting in neurodegeneration, synaptic deficits and the persistent impairment of memory and learning.

The comparison of the effects of propofol and sevoflurane on rat brains in the period of intensive synaptogenesis revealed that a 4.5-hour supply of propofol, as opposed to sevoflurane, caused permanent neurodegenerative changes that persisted for a long time [33]. The differences observed were likely caused by a too-low concentration of sevoflurane, which, similar to earlier observations with isoflurane, begins to exert neurodegenerative effects in concentrations at least threefold higher than those of MAC [33].

Similar effects were demonstrated for morphine, which induces neurodegenerative changes in the selected regions of rat brains (cortex and corpus amygdaloideum) by its antagonist impact on NMDA receptors. The above observation is important, as morphine is used during long-term sedation in neonatal intensive care units (NICUs) [34].

In the last decade, many other experimental studies have been published concerning various anaesthetics, their different doses and times of administration, which to some extent confirmed the earlier findings. A relevant aspect of those studies was the age of the animals, as it is unquestionable that the younger the animal, the greater the neurodegenerative changes. Species differences can hinder the data’s comparison with humans; therefore, the studies were widened to include the 6-day-old Macacus rhesus, which received isoflurane at a concentration of 3MAC for 5 hours. Advanced apoptosis was observed not only in the neurons but also in the glial cells when high concentrations of isoflurane were applied [35].

An extremely interesting issue concerning the permeation of anaesthetics through the placenta and potential neurodegenerative effects is foetal safety during in utero surgical procedures. GABA receptors in adults, as opposed in foetuses, play an inhibitory role. Their stimulating character is associated with an increased concentration of chloride ions inside the nervous cell, generating the depolarisation essential for the activation of neurones, formation of primitive reflexes, and development and differentiation of neurones. The above processes help to prepare and adapt the foetus to delivery-related stress. According to an experimental study in rodents, shortly after delivery, the flow of chloride ions in the ion channels is reversed, and their intracellular content is reduced; hence, the stimulating activity of the GABA receptors changes into an inhibiting function. This phenomenon is affected by oxytocin, which inhibits foetal proteins in the above mechanism, making them less sensitive to damage induced by hypoxia or ischaemia during delivery. Moreover, the neurones can become less sensitive to the neurotoxic effects of anaesthetics. Oxytocin receptor antagonists (atosiban) administered in vivo inhibited the above phenomenon and enhanced anoxic damage to neurones [36].

**CLINICAL TRIALS**

The results of the experimental studies mentioned above induced anaesthesiologists to consider the safety and reversibility of the general anaesthesia used in humans, especially in the early period of life [37]. Many authors have attempted to answer the question as to whether the neurodegenerative changes observed in animal studies occur in humans. The task, however, appears to be more complicated than assumed on the basis of experimental studies, due to clinical difficulties in avoiding disorders of circulatory-respiratory homeostasis during general anaesthesia. Ischaemia caused by the cardiodepressive action of anaesthetics and hypoxia due to their depressive effects on the respiratory system can both lead to similar neurodegenerative...
differences observed between the study and control groups. There were no significant differences in the learning abilities of children delivered by Caesarean section under general anaesthesia and those delivered spontaneously. Interestingly, slightly milder disorders were found in children whose mothers underwent regional anaesthesia for Caesarean section. The authors suggest that short-term exposure to general anaesthetics does not affect long-term neurodevelopmental disorders [38].

Another retrospective cohort study encompassed a group of 5,357 children born in the years 1976–1982. Impaired learning abilities were observed in 932 of the children, and 593 underwent at least one round of general anaesthesia during the first four years of life. The risk of disorders increased with the number of anaesthesia attempts (P < 0.001) [39]. Yet another study involved children who underwent general anaesthesia in the first 24 months of life (group I) or in the period after 24 months of life (group II). Their behavioural patterns were assessed according to the Child Behaviour Checklist/4–18 (CBCL/4-18), distinguishing between the two age periods, i.e., 4–11 and 12–18 years. The incidences of mental disabilities of various severities, problems at school or grade retentions were two times higher in the first group, compared to the second one [40].

Otherwise, DiMagio and co-workers [41] did not find developmental retardation, concentration deficits, language, coordination or behaviour-related disorders among the 306 children who underwent general anaesthesia in the first three years of life out of the 10,450 siblings studied. The authors suggest that such a correlation would occur if several agents of similar neurotoxic potential were used; however, no significant results were presented.

In Denmark, all children are routinely tested at the age of 15–16 years, i.e., 9th grade of their education; these findings enabled a comprehensive analysis of over 2,600 children who underwent hernia repair during infancy. The control group consisted of 14,000 randomly chosen children, representing 5% of the total population of Danish children. All of the participants completed tests scored from 0–13 concerning their knowledge of Danish, foreign languages, mathematics, science and social sciences. There were no differences observed between the study and control groups or female and male genders; all of the children scored a reproducible average of 8 [42].

It is extremely difficult to extrapolate from the results of animal studies to humans due to marked anatomical and physiological differences. For instance, the peak of synaptogenesis in rodents occurs on the 7th day of life and lasts several weeks. In humans, this period is substantially longer, and the most critical period covers the first three years of life.

Despite the above reservations, extremely interesting results were presented in an experimental study with rodents subjected to inhalational anaesthesia whileceiving dexmedetomidine. The findings revealed the protective effects of this treatment for cognitive abilities, learning and memory. Further studies on this aspect of receptor α2 agonist actions could change the current method of paediatric general anaesthesia, favouring the more frequent use of dexmedetomidine. In particular, the pharmacokineti-pharmacodynamic profile of receptor α2 agonists has raised hope for its potentially beneficial clinical effects [43]. Rat newborns were exposed to 0.75% isoflurane concentrations mixed with oxygen or air and received intraperitoneal dexmedetomidine at the doses of 1, 10, 25 μg kg⁻¹ or only at the dose of 25 μg kg⁻¹ in combination with its antagonist, atipamezole, 500 μg kg⁻¹. The activities of the caspases in the various brain regions (cerebral cortex, hippocampus, and thalamus) were assessed immediately, 2 hours and 4 hours after the application of the above agents. The lowest activity of those pro-apoptotic enzymes was observed in the group receiving the highest dose of dexmedetomidine; the highest activity, comparable to that in controls (0.9% NaCl), was found in the group receiving dexmedetomidine and atipamezole simultaneously. According to the authors, the mechanism of neuroprotective action can be explained by the activation of the endogenous α2-noradrenergic system, combined with activation of the pERK-Bcl-2 pathway and factors responsible for the inhibition of neural apoptosis. The activation of the imidazole receptor subtype by the stimulation of other enzymes, e.g., extracellular-signal-regulated kinase (pERK), also initiates an alternative neuroprotective mechanism [44].

In several other laboratory studies, a beneficial protective effect on the CNS has been found after the use of melatonin, lithium, xenon or hyperthermia [45]. Moreover, extra-pharmacological measures, such as strengthening exercises, restrictive diets or progressive environmental effects, may be promising [46, 47].

**SUMMARY**

The results of experimental studies carried out over the last decade demonstrate the cause-effect relationship between the agents used for general anaesthesia versus CNS
damage and developmental impairments in animals. Great caution should be exercised when extrapolating from animal results to humans due to obvious anatomical-physiological differences; additionally, many of the study methods used on animals arouse great controversy (very high concentra-
tions of agents, long exposure times, combinations of many anaesthetics) [48]. The utility of clinical trials is of limited value due to the epidemiological dimensions of data being analysed, which often cover single-centre administrative sources confined to certain geographical regions. Moreover, it should be stressed that apoptosis in the CNS is beneficial, as it enables the development and differentiation of 50–70% of neurons, hence generating necessary changes in brain development. Nevertheless, anaesthesiologists avoid increasingly broad debates on the safety of the agents they use in everyday practice.

In 2011, on the initiative of the International Anesthe-
sia Research Society (IRS) and Food and Drug Adminis-
tration (FDA), international cooperation was undertaken to increase the safety of children undergoing anaesthetic procedures. The initiative was supported by the Ameri-
can Society of Anaesthesiologists (ASA), European Society of Anaesthesiology (ESA), American Academy of Paediatrics (AAP), Society for Neuroscience in Anesthesiology and Criti-
cal Care (SNACC) and Society for Pediatric Anesthesia (SPA). In December 2012, a consensus statement was published, stating “exposure to commonly used anesthetics may produce adverse neurobehavioral effects” and, further, that “in the absence of conclusive evidence, it would be un-
ethical to withhold sedation and anesthesia when neces-
sary” (www.smarrottts.org) [49]. Therefore, it is necessary to continue carrying out on-going retrospective-prospective studies (PANDA [Pediatric Anesthesia and Neurodevel-
opment Assessment], MASK [Mayo Anesthesia Safety in Kids]) and prospective studies (GAS, General And Spinal — Multi-site Randomized Controlled Trial Comparing Regional and General Anesthesia for Effects on Neurodevelopmental Outcome), the first results of which should be expected in 2–3 years. Until that time, the postponement of anaesthetic and surgical procedures in the smallest babies must be considered; wherever necessary, the procedures should be performed as quickly and efficiently as possible. The simultaneous use of various anesthetics of the same neu-
rotoxic potential should be avoided, and patients of this age group should be preferably subjected to local anaesthesia. The above policy should allow us to follow the principles of the Declaration of Helsinki of 2010, highlighting the role of anaesthesiology in promotion of safe perioperative care [50].

References:
4. Shors TJ: Memory traces of trace memories: neurogenesis, synapto-
6. Stahl SM: Disorders of sleep and wakefulness and their treatment in Stahl’s Essential Psychopharmacology. Neuroscientific basis and practi-
11. Corea-Sales C, Robin MC, Maze M: A hypnic responses to desme-
17. Monti JM, Santos H: The roles of dopamine and serotonin, and their recep-
tors, in regulating sleep and waking. Prog Brain Res 2008; 172: 625–646.
22. Overton CE: Studien über die Narkose zugleich ein Beitrag zur allge-
meinen Pharmakologie. Gustav Fischer, Jena, Switzerland 1901.
24. Cantor RS: Breaking the Meyer-Overton rule: predicted effects of varying stiffness and interfacial activity on the intrinsic potency of anesthet-
28. Clayton T, Helmstetter FJ, Furtmüller R et al.: An updated unified phar-
macophore model of the benzodiazepine binding site on gamma-amino-
30. Fredriksen A, Archer T, Álm H et al.: Neurofunctional deficit and po-

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