Isoflurane Versus Desflurane: Haemodynamic Parameters and Recovery Characteristics:

A Comparative Study

Thesis

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Introduction

Inhaled volatile anesthetics remain the most widely used drugs for maintenance of general anesthesia because of their ease of administration and predictable intraoperative and recovery characteristics. Management of haemodynamic stability and early recovery is the most important part of a standardized balanced technique. Given the low blood-gas partition coefficients of isoflurane (1.4) and desflurane (0.42), a more rapid emergence from anesthesia is expected compared with traditional inhalation anesthetics ***(Nathanson et al., 1995).***

Isoflurane is a clear, colourless, volatile, halogenated, non-flammable liquid which induces and maintains general anesthesia by depression of the central nervous system and resultant loss of consciousness ***(Rang et al.,2003).***

Isoflurane is an inhalational anesthetic whose low solubility (blood/gas partition coefficient equals 1.4) permits a rapid induction of and recovery from anesthesia. The mild pungency of isoflurane may limit the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. The level of anesthesia may be

changed rapidly with isoflurane. Pharyngeal and laryngeal reflexes are readily and easily obtunded ***(Eger et al., 2003).***

Isoflurane is a profound respiratory depressant. An increase in anesthetic dose will decrease tidal volume without changing respiratory rate. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia ***(Eger et al., 2003).***

Desflurane (2, 2, 2-trifluoro - 1- fluoroethyl-difluoromethyl ether) is a highly fluorinated methyl ethyl ether used for maintenance of general anesthesia. It is gradually replacing isoflurane for human use. It has the most rapid onset and offset of the volatile anesthetic drugs used for general anesthesia due to its low solubility in blood ***(Tsai et al.,1992).***

Desflurane is a colorless, volatile, nonflammable liquid administered via vaporizer specifically designated for its use as a general inhalation anesthetic; it is volatile liquid below 22.8°C. Data indicate that desflurane is stable when stored under normal room lighting conditions according to instructions ***(Larsen et al., 2000).***

Aim of the work

The purpose of this study was to compare the hemodynamic, emergence and recovery characteristics of isoflurane with those of desflurane in general anesthesia for patients going to pelvi-abdominal operations.

Mechanism of Action of General Anesthesia

A general anesthetic is a drug that brings about a reversible loss of consciousness. These drugs are generally administered by an anesthetist in order to induce or maintain general anesthesia to facilitate surgery ***(Cameron, 2006).***

General anesthetics have been widely used in surgery since 1842 when Crawford Long for the first time administered diethyl ether to a patient and performed a painless operation. It has always been believed that general anesthetics exert their effects (analgesia, amnesia, immobility) by modulating the activity of membrane proteins in the neuronal membrane. However, the exact location and mechanism of this action are still largely unknown although much research has been done in this area. There are a number of outdated and modern theories that attempt to explain anesthetic action ***(Cameron, 2006).***

1- Lipid solubility-anesthetic potency correlation (the Meyer-Overton correlation)

- ***Outdated lipid hypotheses of general anesthetic action***

The nonspecific mechanism of general anesthetic action was first proposed by Von Bibra and Harless in 1847. They suggested that general anesthetics may act by dissolving in the fatty fraction of brain cells and removing fatty constituents from them, thus changing activity of brain cells and inducing anesthesia. In 1899 Hans Horst Meyer published the first experimental evidence of the fact that anesthetic potency is related to lipid solubility ***(Franks and Lieb, 1978).***

Meyer compared the potency of many agents, defined as the reciprocal of the molar concentration required to induce anesthesia in tadpoles, with their olive oil/water partition coefficient. He found a nearly linear relationship between potency and the partition coefficient for many types of anesthetic molecules such as alcohols, aldehydes, ketones, ethers, and esters. The anesthetic concentration required to induce anesthesia in 50% of a population of animals was independent of the means by which the anesthetic was delivered ***(Franks and Lieb, 1978).***

Meyer and Overton had discovered the striking correlation between the physical properties of general anesthetic molecules and their potency: the greater is the lipid solubility of the compound in olive oil the greater is its anesthetic potency. This correlation is true for a wide range of anesthetics with lipid solubilities ranging over 4-5 orders of magnitude if olive oil is used as the oil phase. However, this correlation can be improved considerably in terms of both the quality of the correlation and the increased range of anesthetics if bulk octanol or a fully hydrated fluid lipid bilayer is use d as the oil phase. It was noted also that volatile anesthetics are additive in their effects (a mixture of a half dose of two different volatile anaesthetics gave the same anesthetic effect as a full dose of either drug alone) ***(Vaes et al., 1997).***

2- Modern lipid hypothesis of general anesthetic action

The modern version of lipid hypothesis states that anesthetic effect happens if solubilization of general anesthetic in the bilayer causes a redistribution of membrane lateral pressures ***(Eckenhoff et al., 1999).***

Each bilayer membrane has a distinct profile of how lateral pressures are distributed within it. Most membrane proteins especially ion channels are sensitive to changes in this lateral pressure distribution profile. These lateral stresses are

rather large and vary with depth within the membrane. According to the modern lipid hypothesis a change in the membrane lateral pressure profile shifts the conformational equilibrium of certain membrane proteins known to be affected by clinical concentrations of anesthetics such as ligand-gated ion channels. This mechanism is also nonspecific because the potency of the anesthetic is determined not by its actual chemical structure, but by the positional and orientational distribution of its segments and bonds within the bilayer. However, it is still not obvious what the exact molecular mechanism is. It was proposed that incorporation of amphiphilic and other interfacially active solutes (e.g. general anesthetics) into the bilayer increases the lateral pressure selectively near the aqueous interfaces, which is compensated by a decrease in lateral pressure toward the centre of the bilayer. Calculations showed that general anesthesia likely involves inhibition of the opening of the ion channel in a postsynaptic ligand-gated membrane protein ***(Mohr et al., 2005).***

Thus, according to the modern lipid hypothesis anesthetics do not act directly on their membrane protein targets, but rather perturb specialized lipid matrices at the protein-lipid interface, which act as mediators. This is a new kind of transduction mechanism, different from the usual key-

lock interaction of ligand and receptor, where the anesthetic (ligand) affects the function of membrane proteins by binding to the specific site on the protein. Thus, some membrane proteins are proposed to be sensitive to their lipid environment ***(Cantor, 2001).***

2- Membrane protein hypothesis of general anesthetic action

Inhaled general anesthetics frequently do not change structure of their target protein but change its dynamics especially dynamics in the flexible loops that connect α-helices in a bundle thus disrupting modes of motion essential for the protein function ***(Cui et al., 2008).***

In the early 1980s, Franks and Lieb demonstrated that the Meyer-Overton correlation can be reproduced using a soluble protein. They found that two classes of proteins are inactivated by clinical doses of anesthetic in the total absence of lipids. These are luciferases, which are used by bioluminescent animals and bacteria to produce light, and cytochrome P450, which is a group of heme proteins that hydroxylate a diverse group of compounds, including fatty acids, steroids, and xenobiotics such as phenobarbital. Remarkably, inhibition of these proteins by general anesthetics

was directly correlated with their anesthetic potencies ***(Ma et al., 2008).***

These observations were important because they demonstrated that general anesthetics may also interact with hydrophobic protein sites of certain proteins, rather than affect membrane proteins indirectly through nonspecific interactions with lipid bilayer as mediator. It was shown that anesthetics alter the functions of many cytoplasmic signalling proteins, including protein kinase C, however, the proteins considered the most likely molecular targets of anesthetics are ion channels. According to this theory general anesthetics are much more selective than in the frame of lipid hypothesis and they bind directly only to small number of targets in Central nervous system mostly ligand(neurotransmitter)-gated ion channels in synapse and G-protein coupled receptors altering their ion flux. General anesthetics can inhibit the channel functions of excitatory receptors or potentiate functions of inhibitory receptors, respectively. Although protein targets for anesthetics have been partly identified the exact nature of general anesthetic-protein interactions still remains a mystery ***(Canals et al., 2008).***