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Do Inhalational Anesthetic Agents Still Hold Their Place in Modern Anesthesia Practice?

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ABSTRACT

Inhalational anesthetic agents are chemical substances that are administered into the body via lungs and distributed to organs and tissues by blood circulation. The main site of their action is the brain, but they also affect other parts of central nervous system. Volatile and intravenous anesthetics alike have nearly reached the characteristics of an ideal anesthetic, but at a first glance, the increase in use of intravenous anesthetics could likely push out their volatile counterparts. Looking at the situation more thoroughly, positive side effects of volatile anesthetics that are not found in their intravenous counterparts, still give them a place in modern anesthesia practice. It is also possible to combine both techniques to reduce negative adverse effects, while making use of the positive ones.

INTRODUCTION

Inhalational anesthetic agents are chemical substances administered into the body via lungs and distributed to organs and tissues by blood circulation. The main site of their action is the brain, but they also affect other parts of central nervous system. In the brain, they act on the membranes of neurons. They can facilitate inhibitory functions or attenuate excitation of neurons, which can result in general anesthesia.

The characteristics of an ideal anesthetic agent should include: rapid induction and emergence, simple use, sufficient analgesia, inhibition of reflexes and relaxation of striated muscles, safety and absence of toxic adverse effects.

Volatile anesthetics used today have come close to the above described criteria, but do not fulfill them completely just yet. For these reasons, we combine them with other medications (intravenous anesthetics, opioids, nitrogenous oxide, muscle relaxants). Most often, we use them in so called "balanced anesthesia". This way, safety is increased, while negative adverse effects are decreased.

Recently, TCI (target-controlled anesthesia) with intravenous anesthetics is being used more and more. It would appear that intravenous anesthetics are going to completely push out the volatile anesthetics that had been used a lot in the past. But is this really going to happen?

IS THE NONSPECIFIC MECHANISM OF ACTION THE MAIN ADVANTAGE OF VOLATILE ANESTHETICS?

Intravenous anesthetics in use today, such as propofol and etomidate, work mainly by acting on GABA receptors. Relatively high selectivity of these compounds is apparent, when replacing one amino acid in the GABA receptor. That can already counter the effects of an intravenous anesthetic. Because of this high selectivity, intravenous anesthetics have generally less adverse effects in comparison to volatile anesthetics. There is also a possibility for development of selective antagonists, such as flumazenil for benzodiazepines.

High selectivity is not necessarily an advantage, though. For example, a minor mutation in a patient could decrease efficacy of intravenous anesthetic. Such mutations had already been proven. Expression of GABA receptor itself, for example in alcohol consumption or neurologic disorder, could also change the sensitivity for an intravenous anesthetic. In volatile anesthetics we do not encounter such phenomena. Even though they act on GABA receptors as well, they produce anesthesia by acting on different sites. If it turns out, that when propofol is not efficient in a patient, volatile anesthetics present an excellent alternative and can produce sufficient depth of anesthesia (1).

There is also a difference between volatile and intravenous anesthetics in their effect on nociceptive and other neural pathways in the spinal cord. Intravenous anesthetics ensure good anesthesia and amnesia, but they do not affect other structures in the spinal cord. Increased intake of propofol does not result in increased muscle relaxation, as opposed to volatile anesthetics. That results in more frequent muscle contractions and movements with propofol. Intravenous anesthetics possibly inhibit spinal neurons that express GABA. This could increase excitability of spinal neural networks. Studies have shown that volatile anesthetics attenuate motor response to pain stimulus via glycine receptors. Glycine is, in fact, one of the main actors in spinal pain processing. Volatile anesthetics are the only substances that have a modulatory effect on glycine receptors in clinically relevant doses (1).

It is also very desirable for a modern anesthetic to work by attenuating pain in the spinal cord aside from its anesthetic and anamnestic properties. That could decrease the chance of hyper-sensibilization and chronic pain development (1).

These characteristics could make volatile anesthetics model compounds for development of new intravenous anesthetics. Modern intravenous anesthetics should, aside from their action on GABA receptors, influence the glycine receptors as well. Such anesthetic agents are already being developed in laboratories.

Development of intravenous agents that would work less specifically and on multiple different receptors contradicts the principle that anesthetic substances should have a specific mechanism of action (2). In the past, highly selective substances had been synthetized, but have resulted in unexpected consequences (3, 4). A possible reason for that in biologic organisms could lie in their need for stability, result-

ing in development of multiple copies of signaling pathways or production of compensatory mechanisms to counter the external disturbance. A more recent view in development of the new medications is not concentrated on highly selective drugs that would work on a specific receptor anymore but rather on developing substances that trigger the molecular mechanism and work on interactions of signaling pathways- i.e. network pharmacology (4, 5).

IMMUNOMODULATORY ACTION OF VOLATILE ANESTHETICS

Another reason for usage of volatile anesthetics is their beneficial immunomodulatory and anti-inflammatory effect. Many studies have shown that volatile anesthetics reduce systemic and local inflammatory response during major surgery (6, 7).

Cellular- protective effects of volatile anesthetics had first been proven in cardiovascular surgery. Volatile anesthetics have proven cardio-protective effect and have been applied for pre-and post-conditioning in open cardiac surgery with extracorporeal circulation (8).

Later, evidence of volatile anesthetics' beneficial effects had emerged in other surgical fields as well. In UMC Ljubljana, Jerin et al. showed decreased perioperative inflammation, when using volatile anesthetics in patients undergoing liver surgery (9). Perioperative inflammatory response is dependent mainly on the type of anesthetic substance used. Lahat and McBridge showed in their studies, increased levels of cytokines in the blood immediately following induction, before the beginning of surgical procedure (10, 11). Studies on cell cultures implied, that intravenous anesthetics encourage inflammatory cells to produce cytokines (12). Intravenous anesthetics inhibit polarization of neutrophils and chemotaxis to a greater extent than their volatile counterparts. (13) Anesthetics do not only change non-specific, but also specific immune response by affecting proliferation, lymphocyte count and levels of immunoglobulins in blood (14).

Limited animal data have suggested that volatile anesthetics can induce neuro-inflammation, which leads to the decline of cognitive function in rodents. This effect is yet to be verified in humans (15). However, volatile anesthetics have been shown to accelerate post-ischemic neurogenesis, suggesting that they may also enhance endogenous reparative processes in the injured brain (16).

ANESTHETICS AND INFLAMMATORY RESPONSE

In general, anesthetic agents cause an increase in production and levels of leukocytes in blood (17). Every anesthetic affects a different type of immune cells (Table 1) (17).

Anesthetic agents also affect perioperative immune response with their effect on synthesis and excretion of cytokines and glucocorticoids (Table 2) (17).

General anesthetics and inflammation Propofol reduces production of pro-inflammatory cytokines, alters expression of nitric oxide, and inhibits neutrophil function (18). Researchers have been studying pro-inflammatory effects of propofol for a long time, but so far, no published study has yet confirmed it. Inflammation could be a result of apolipoprotein A-1 modulation. Ricou was the latest to start a study that would explore this, but there have been no published results yet (19-21).

Aside from anesthesia, volatile anesthetics have other effects. Of those, inhibition of inflammatory response is especially important and beneficial (22). That was first shown by in vitro studies on animals (23). Subsequent clinical studies have confirmed that, at first in the field of cardiac surgery. It was proven that sevoflurane, when used in extracorporeal circulation, decreases expression of antigen receptor in granulocytes and polymorphonuclear (PMN) cells. Following studies showed decreased blood levels of pro- inflammatory cytokines (especially TNF-α, IL-6 and IL-8) after using extracorporeal circulation (24). A study from this field was undertaken in Slovenia as well and it confirmed the beneficial effect of volatile anesthetics in cardiac surgery (25).

Anti-inflammatory characteristics of volatile anesthetics had also become a point of interest in the field of thoracic surgery, where postoperative pulmonary inflammation is the main reason of perioperative morbidity and mortality. Studies have shown beneficial effects of volatile anesthetics in sense of postoperative inflammation decrease and decrease of postopera-

Table 1. General anesthetics and their effect on immune cells.

Immune cell	Effect
Leukocytes	sevoflurane ↑ cell count, desflurane ↑ cell count, propofol ↑ cell count, isoflurane ↑ cell count
Neutrophiles	thiopental ↓ phagocytosis, propofol ↓ phagocytosis ↑ cell count, isoflurane ↓ phagocytosis, desflurane ↑ cell count
Mononuclear phagocytes	sevoflurane ↓ monocyte count, halothan ↑ phagocytosis ↓ cell count, propofol ↓ phagocytosis , midazolam ↓ phagocytosis, thiopental ↓ phagocytosis
Lymphocytes	propofol ↓ cell count, sevoflurane ↓ cell count, isoflurane ↓ cell count, ketamine ↓ proliferation
Natural killer cells	propofol ↑ cell count, ↓ cytotoxic activity sevoflurane ↑ cell count, desflurane ↑ cell count, isoflurane ↓ cell count, halothane ↓ cytotoxic activity
CD4 T-helper cells	halothane ↓ cell count, sevoflurane ↓ cell count, isoflurane ↓ cell count, propofol ↑ cell count
CD8 cytotoxic T-lymphocytes	propofol ↓ cell count, sevoflurane ↓ cell count, halothane ↓ cell count, isoflurane ↑ cell count, desflurane ↑ cell count, isoflurane ↑ apoptosis
CD19 B-lymphocytes	isoflurane ↑ cell count, desflurane ↑ cell count , halothane ↑ antibody titre, sevoflurane ↑ primary and secondary immune response

Table 2. Effects of general anesthetics on cytokine synthesis.

Cytokine	Effect on plasma levels
IL-1	propofol ↓, ketamine ↓, thiopental ↓, isoflurane ↑, sevoflurane ↓, desflurane ↓
IL-6	propofol ↑, ketamine ↓, thiopental ↓, remifentanil ↑, sevoflurane ↑, isoflurane ↑
IL-8	ketamine ↓, propofol ↑ , thiopental ↓, midazolam ↓, isoflurane ↑ , propofol in vitro ↓ excretion from neutrophiles
IL-10	ketamine ↑ , propofol ↑ , thiopental ↑, isoflurane ↑, sevoflurane ↑
TNF-α	ketamine ↓, propofol ↓, thiopental ↓, isoflurane ↑, sevoflurane ↓, enflurane ↓

tive complications (26).

On the other hand, study on patients undergoing craniotomy showed that propofol based anesthesia was associated with significantly higher anti-inflammatory cytokine IL-10 levels than anesthesia with sevoflurane. These findings, however, seem to have little effect on outcome, since neither sevoflurane nor propofol had any significant impact on the occurrence of postoperative complications (27). Therefore, in general, it is possible to assert that inhalational and intravenous anesthetic agents, obviously with some minor exceptions, might play an important role in terms of neuroprotection during surgical procedures. Nevertheless, data seem to be insufficient to recommend any specific anesthetic agent as the optimal neuroprotective agent (28).

CONCLUSION

At present, available experimental data do not support the selection of any one anesthetic agent over the others. Modern intravenous anesthetic agents are substances that get very close to a theoretical ideal anesthetic, but volatile anesthetics still hold a place in modern anesthesia practice. Aside from anesthesia and amnesia they also have analgesic properties and muscle relaxant effect. Their beneficial immunomodulatory effect and anti-inflammatory effect is desirable especially in major surgical procedures, linked to substantial systemic inflammatory response in the perioperative period. Lastly, both anesthetic techniques can be combined (intravenous and inhalational anesthesia). That increases the desirable effects of both agents, while decreasing their adverse effects.

Conflicts of Interest

The authors declare no conflicts of interest.

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