

INTERACTIONS BETWEEN INHALED ANESTHETICS AND CYTOSTATIC AGENTS

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Summary

Inhaled anesthetics are often used for inducing or maintaining anesthesia in cancer patients as the length and complexity of the surgical procedure cannot be predicted for it depends on intraoperative surgical and pathohistological findings, and as often as not requires repeated operations for removal or reduction of the primary tumor, regional metastases, recurrence, pathological fractures, or surgery complications. These are easily volatile liquids that enter the body through inhalation, and then, by diffusion through the alveolocapillary membrane, they are transferred into the blood stream to be transported to all other organs and the central nervous system. Most of the inhaled anesthetics are eliminated from the body through respiration; a portion of them, however, metabolizes in the liver via the cytochrome P450 oxidase family and is excreted via the kidneys, so the issue of their toxicity has always attracted a considerable interest from investigators. Cancer patients receiving cytostatic agents during the perioperative period increase in number every day. Aside from their planned surgery, cancer patients receiving cytostatics also undergo emergency surgery either for their disease complication or for another reason. It is important to understand the pharmacology of cytostatics, their interaction with anesthetics, pharmacokinetics and toxic reactions. Cytostatics and general anesthetics act immunosuppressively and thus compromise the patient's immune status. In addition, cytostatics depress the myocardium and damage lung function, which can cause serious problems during anesthesia. Each anesthesia as well as each surgery produce stress on the body, and the anesthetics themselves alter the cell immunity so the patients receiving cytostatics during their perioperative period can experience serious general and organ-specific side effects. It would be worth knowing whether any of the most commonly used anesthetics today show an advantage in treating patients with cancer, especially patients receiving chemotherapy, and whether the inhaled anesthetics combined with cytostatics increase, enhance or even suppress the individual effect on various types of cells, above all on tumor cells that can become resistant to therapy for developing the so-called „multidrug resistance“.

KEY WORDS: *inhaled anesthetic agents, cytostatic agents, drug interaction*

INTERAKCIJA INHALACIJSKIH ANESTETIKA I CITOSTATIKA

Sažetak

Inhalacijski anestetici često se primjenjuju za uvod u anesteziju ili za održavanje anestezije kod onkoloških bolesnika zbog toga što se kod uvida u anesteziju dužina i opseg operacijskog zahvata često ne mogu predvidjeti i ovise o intraoperacijskom kirurškom i patohistološkom nalazu, a nerijetko su potrebne ponavljane operacije zbog uklanjanja ili

redukcije primarnog tumora, regionalnih metastaza, recidiva bolesti, udaljenih metastaza, patoloških fraktura ili zbog komplikacija same operacije. To su lako hlapljive tekućine koje u organizam ulaze udisanjem, a zatim difuzijom kroz alveolokapilarnu membranu prelaze u krvotok, krvotokom se dopremaju do svih ostalih organa i do središnjeg živčanog sustava. Veći dio inhaliranih anestetika se eliminira iz organizma respiracijom, međutim jedan dio metabolizira se u jetri putem obitelji citokrom oksidaza P450 i izlučuje putem bubrega te je pitanje njihove toksičnosti od uvijek izazivalo veliki interes istraživača. Svakodnevno se povećava broj onkoloških bolesnika koji primaju citostatike u periperacijskom periodu primaju citostatike. Osim planiranih operacijskih zahvata onkološki bolesnici koji primaju citostatike podvrgavaju se i hitnim operacijskim zahvatima, bilo zbog komplikacija bolesti ili zbog nekog drugog razloga. Važno je razumjeti farmakologiju citostatika, interakciju s anestetima, farmakokinetiku i toksične reakcije. Citostatiki i opći anestetici djeluju imunosupresivno na bolesnika te kompromitiraju njegov imunološki status. Osim toga, citostatiki deprimiraju miokard i oštećuju plućnu funkciju, što može izazvati ozbiljne probleme u anesteziji. Svaka anestezija i operacija predstavlja stres za organizam, a sami anestetici mijenjaju staničnu imunost, te bolesnici koji primaju citostatike u perioperacijskom periodu mogu imati ozbiljne opće i organ specifične nuspojave. Bilo bi dobro znati ima li neki od danas najčešće upotrebljivanih anestetika prednost u primjeni kod onkoloških bolesnika, osobito ako ti bolesnici primaju citostatike te da li inhalacijski anestetici i citostatiki u kombinaciji povećavaju, potenciraju ili čak suprimiraju pojedinačni učinak na različite vrste stanica, osobito tumorskih stanica koje mogu postati rezistentne na terapiju zbog tzv. „multidrug resistance“.

KLJUČNE RIJEČI: *inhalacijski anestetici, citostatiki, interakcija lijekova*

INTRODUCTION

Pharmacokinetic drug interactions occur when a drug alters the disposition of another by affecting the drug levels either in blood or on the receptor. The altered drug level on the receptor can result from the altered drug absorption, distribution, metabolism, removal or excretion.

INHALED ANESTHETIC AGENTS

Considering their numerous advantages, inhaled anesthetics are very often used for inducing or maintaining anesthesia. They are especially eligible for anesthesia in cancer patients as at their anesthesia induction, the length and complexity of the surgical procedure often cannot be predicted for it depends on intraoperative surgical and pathohistological findings, and as often as not requires repeated operations for removal or reduction of the primary tumor, regional metastases, recurrence, distant metastases, pathological fractures, or surgery complications.

Since recently in Croatia the most commonly used inhaled anesthetic has been halothane, and today there are isoflurane and sevoflurane. These are easily volatile liquids that enter the body through inhalation, and then, by diffusion through the alveolocapillary membrane, they are transferred into the blood stream to be transported to all other organs and the central nervous system. Most of the inhaled anesthetics

are eliminated from the body through respiration; a portion of them, however, metabolizes in the liver via the cytochrome P450 oxidase family and is excreted via the kidneys, so the issue of their toxicity has always attracted a considerable interest from investigators (1).

Inhaled anesthetics are not biochemically inert compounds. They metabolize *in vivo* and their metabolites may cause acute or chronic toxicity. The main mechanisms of toxicity include the intracellular accumulation of metabolites, formation of haptens that may produce systemic hypersensitivity or immunological response, and formation of reactive metabolites which can covalently bind to tissue macromolecules or produce destructive free radicals. Binding of inhaled anesthetic reactive metabolites to tissue proteins can lead to the formation of hapten-protein conjugates. These conjugates can lead to the synthesis of specific antibodies and thus provoke an immunological response. In normal conditions, glutathione and sulfhydryl contents have a role of normal cellular antioxidants that conjugate free radicals, but in case of their lack, the destructive activity proceeds and finally results in cell death. Considering the lipophilic nature of inhaled anesthetics, the greatest damage produced by their free radicals occurs in lipid membranes, resulting in peroxidation and the separation of hydrogen from the α -methylene carbon atom in fatty acids (2).

INTERACTION BETWEEN INHALED ANESTHETICS AND CYTOSTATICS

Cancer patients receiving chemotherapy during the perioperative period increase in number every day. Chemoperfusion is a new clinical oncology technique; the procedure includes intraoperative infusion of cytostatics administered intraperitoneally or into specific organs, i.e. liver, spleen or any other tumor-invaded regions.

Aside from their planned surgery, cancer patients receiving cytostatics also undergo emergency surgery either for their disease complication or for another reason. With a growing number of cancer patients the number of serious complications resulting from the interaction between anesthetic and cytostatic agents is also rising. The literature coverage of this topic is rather low, so one would understand that this interaction does not represent a great clinical problem, although, however, a lack of knowledge and understanding does not diminish the importance of pharmacological interactions occurring between anesthetics and cytostatics (3). Cytostatic agents are extremely reactive compounds that are usually administered in combinations targeting all fast-dividing cells (not only tumor cells) and thus resulting in high toxicity (4). It is very important to understand the pharmacology of cytostatics, their interactions with anesthetics, pharmacokinetics and toxic reactions. Inhaled anesthetics reduce the flow of blood through the liver, binding to plasma proteins, and activity of metabolic enzymes and thus inhibit metabolism of a large number of drugs (5). Cytostatics and general anesthetics act immunosuppressively and thus compromise the patient's immune status. In addition, cytostatics depress the myocardium and damage lung function, which can cause serious problems during anesthesia.

Each anesthesia as well as each surgery produce stress on the body, and the anesthetics themselves alter the cell immunity so the patients receiving cytostatic drugs during their perioperative period can experience serious general and organ-specific side effects. Cancer patients often have increased chromosome instability before the onset of treatment compared to healthy individuals. In the paper by Kopjar et al., increased cytogenetic damage in peripheral blood lympho-

cytes was reported in tumor patients; the cause may be in the DNA repair ability damage or these patients' more sensitive DNA compared to healthy individuals (6). Symptoms not visible at first sight may develop and lead to complications during anesthesia, in the postoperative period or long after the patients recovers from surgery and chemotherapy and resumes his daily activities. The most common early side effects include gastrointestinal side effects, damage to the liver, kidney and central nervous system, and myelosuppression. Cisplatin may cause damage to the proximal tubules, increased excretion of sodium and electrolyte disorder, and dose-dependent neurotoxicity (6). The effects of interaction between inhaled anesthetics and cytostatic drugs can also be seen after a longer period of remission as these patients are at increased risk of developing secondary cancers, including leukemia and solid tumors. For that reason, patients with malignancy require the follow-up biomonitoring after receiving therapy (6).

Cytostatic agents are drugs aimed at selectively destroying tumor cells interfering with their metabolism. They metabolize via the P450 enzyme system in the liver and some other tissues, and are excreted via kidneys. Inhaled anesthetics are commonly eliminated from the body via lungs, however, their smaller portion metabolizes in the liver, also via the cytochrome P450. The cytochrome P450 is composed of over fifty enzymes that are responsible for the Phase I metabolism of many drugs. Inhaled anesthetics, halothane in particular, reduce the flow of blood through the liver and kidneys, and thus also alter metabolism of cytostatic drugs. Apart from their interference with metabolism of cytostatic drugs to alter cytostatic toxicity, the inhaled anesthetics also affect the growth of tumor cells (7).

Both genotoxicity and cytotoxicity of cytostatic agents are indisputable, they show the cytostatic mechanism of action, but the standpoints regarding genotoxic and cytotoxic effects of the inhaled anesthetics are, however, different. Studies to date show toxicity in the operating room staff chronically exposed to inhaled anesthetics and their effect on the reproductive function (8). The statistically significant larger number of chromosome aberrations and micronuclei has been substantiated, as well as an increased

rate of sister chromatid exchanges in peripheral lymphocytes of the operating room staff (9-11). Matsuoka et al. (12) show *in vitro* that sevoflurane and isoflurane enhance apoptosis in peripheral lymphocytes depending on the dose and exposure times to these anesthetics, and apoptotic signaling pathway activated by sevoflurane include damage to the mitochondrial membrane and release of cytochrome c from the mitochondrion into the cytosol. In contrast, Tyther et al. (13, 14) confirmed that isoflurane and sevoflurane inhibit dose-dependent apoptosis of polymorphonuclear neutrophils *in vivo* and *in vitro*. Moudgil et al. (15) showed that equipotent concentrations of isoflurane, enflurane, halothane and methoxyflurane combined with 70% nitrous oxide affect the chemostatic migration of neutrophils and monocytes. They showed that, with the exception of isoflurane, other inhaled anesthetics reduce chemostatic migration of these cells, nitrous oxide at the most.

There are numerous *in vitro* studies investigating the effect of inhaled anesthetics chiefly on peripheral lymphocytes, and also on other cell types. However, *in vivo* studies, both on animal and human models, are rather rare. Morisaki et al. (16) showed that although the total number of leukocytes does not alter after anesthesia with sevoflurane, the number of neutrophils decreases and lymphocytes increase. Unlike these results, Puig et al. (17) showed that after anesthesia with 3% sevoflurane in mice, sevoflurane alters the total number of peripheral leukocytes, B lymphocytes, CD4+ cells, immune response to sheep erythrocytes, but without any hepatotoxicity or nephrotoxicity. Comparing the genotoxicity of sevoflurane and isoflurane in patients' peripheral blood lymphocytes before and after anesthesia using the comet assay, it was shown that both agents have a potent genotoxic effect. The effect is at its peak 120 minutes after anesthesia, and DNA repair activity starts on day 3 after anesthesia to reach its completion on day 5 (18). Alleva et al. (19) studied DNA damage, DNA repair enzyme and apoptosis in human lymphocytes after anesthesia with sevoflurane. They demonstrated that the highest level DNA damage occurs on postoperation day 1 with the DNA repair process starting after 24 h already; in the cells beyond repair, the mechanism of apoptosis is initiated.

Much less studies have investigated the effect of inhaled anesthetics on tumor cells. Kvolik et al. (20) demonstrated that halothane, isoflurane and sevoflurane in anesthetic doses have cytotoxic and antiproliferation effects on tumor cells *in vitro*. Moudgil and Singal (21) showed that halothane and isoflurane increase the number of lung metastases in C57B1 mice with melanoma, and Melamed et al. (22) demonstrated on rats that halothane results in immunosuppression due to reduced activity of natural killer cells. Hack et al. (23, 24) showed that Ehrlich ascites tumor cells are appropriate to investigate the effects of inhaled anesthetics and reported that a long-term cell exposure to halothane, isoflurane and enflurane, these agents show cytostatic activity *in vitro*.

CONCLUSION

The genotoxic and cytotoxic effects of the inhaled anesthetics in combination with cytostatics on peripheral blood, liver, kidney, brain and tumor cells can only be hypothesized, although their understanding would be very useful for everyday clinical practice. It would be worth knowing whether any of the most commonly used anesthetics today show any advantage when used in patients with cancer, especially patients receiving chemotherapy, and whether the inhaled anesthetics combined with cytostatics increase, enhance or even suppress the individual effect on various types of cells, above all on tumor cells that can become resistant to therapy for developing the so-called „multidrug resistance“ (25). As it is very difficult to conduct clinical trials of the type, most of the information available rely on results of *in vitro* studies of cultures of human tumor cells or *in vivo* in animal models. In addition, it would be useful to determine the combined effect of inhaled anesthetics and cytostatic drugs on hematological and biochemical blood parameters, taking into consideration toxicity of formed metabolites that require further investigation.

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