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REVIEW

The Use of Muscle Relaxants After Chemotherapy and Radiotherapy

Paweł Radkowski[1–3], Michał Jacewicz[2], Iwona Podlińska[2], Maria Derkaczew[2]

[1]Department of Anaesthesiology and Intensive Care, Regional Specialist Hospital in Olsztyn, Olsztyn, Poland; [2]Department of Anaesthesiology and Intensive Care, Faculty of Medicine, Collegium Medicum University of Warmia and Mazury in Olsztyn, Olsztyn, Poland; [3]Department of Anaesthesiology and Intensive Care, Hospital zum Heiligen Geist in Fritzlar, Fritzlar, Germany

Correspondence: Maria Derkaczew, Department of Anaesthesiology and Intensive Care, Faculty of Medicine, Collegium Medicum University of Warmia and Mazury in Olsztyn, Olsztyn, Poland, Email m.derkaczew@gmail.com

Introduction: Patients after chemotherapy and radiotherapy while being operated can suffer from different systemic problems, which may complicate the anesthetic management. Some interactions between muscle relaxants and chemotherapeutics can occur.

Aim: This article aims to present the use of muscle relaxants in cancer patients who have undergone chemotherapy and radiotherapy.

Material and Methods: Our work is based on the available literature and the authors' experience.

Conclusion: Based on our observations and a thorough examination of the medical literature, it is advisable to exercise significant caution when employing muscle relaxants in individuals undergoing chemotherapy and radiotherapy. All muscle relaxants can behave differently after chemotherapy and radiotherapy, and for this reason, practitioners should familiarize themselves with the pharmacodynamics and pharmacokinetics of their chosen muscle relaxant.

Keywords: muscle relaxant, chemotherapy, radiotherapy

Introduction

Cancer ranks as the second leading cause of death worldwide and poses a formidable challenge in terms of treatment. Available treatment modalities for different types of cancers encompass a range of approaches, including surgery, radiation, and chemotherapy. The objective of chemotherapy is to induce cellular damage in rapidly proliferating cells.[1] Radiotherapy involves administering concentrated and consistent doses of ionizing radiation to address diverse malignant conditions. The goal of radiotherapy is to deliver the maximum radiation dose to the tumor while minimizing damage to surrounding healthy tissues. Administering anesthesia to cancer patients necessitates comprehension of potential drug interactions between anesthetics and cytotoxic agents.[2]

Patients after radio- and chemotherapy treatments suffer from physical side effects, such as fatigue, hair loss, nausea, vomiting, and weight loss, but also many problems which may significantly change the anesthesiologist's approach. The main problems of an anesthesiologist in cancer patients are as follows: cardiovascular (pericardial effusion, cardiomyopathy, arrhythmia), pulmonological (pleural effusion, atelectasis, pulmonary dysfunction), gastrointestinal (nausea, diarrhea, enterocolitis, hepatitis, liver damage), renal (acute kidney injury, chronic kidney disease, proteinuria, nephrotic syndrome), hematopoietic (anemia, granulocytopenia, thrombocytopenia, hypercoagulability), metabolic (hypoglycemia, hypercalcemia, hypocalcemia, hyperkalemia, hypertension, SIADH, Cushing syndrome), neurological (neuropathy, myasthenia, metastases in the brain and spinal cord) and oncological treatment interactions.[3–5]

A patient under general anesthesia should be appropriately monitored for many factors, including electrocardiogram (ECG), temperature, non-invasive blood pressure (NIBP), capnography, respiratory rates, and other measurements relevant to the surgeon's performance and the safety of the patient on the operating table When muscle relaxants are being used perioperative management of neuromuscular blockade is conducted. The evaluation of the adductor pollicis response to train of four (TOF) at the ulnar nerve remains the gold standard for intraoperative stimulation. The recovery of about 10% of initial muscle strength is indicated by the presence of 1 to 2 responses for TOF stimulation.[6,7]

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Radiochemotherapy often causes changes in human physiology and thus it also causes alterations in the distribution of muscle relaxant drugs administered to patients. This paper presents the most common side effects of radio and chemotherapy that may affect the duration and activity of muscle relaxants, as well as possible cancer type – muscle relaxant relation and preference of choosing one other another in certain types of cancers.[8]

Materials and Methods

The work is based on the available literature and the author's experience. The purpose of this article is to present the use of muscle relaxants after chemotherapy and radiotherapy.

The search was conducted on electronic databases such as Embase, PubMed, Google Scholar, Scopus, Web of Science, and Cochrane Library yielded relevant articles using valid keywords. A total of 33 articles published between 1963 and 2023 were identified for inclusion in our review. The search terms "muscle relaxants" in conjunction with "radiotherapy" or "chemotherapy" were employed. Articles meeting the criteria were then independently included in the research process.

We have meticulously considered both recent publications and foundational principles of anesthesiology. Many earlier articles were included in this study because there is a scarcity of recent reports on specific muscle relaxants, likely attributed to their infrequent use in current practice. Special attention was given to the clinical aspects of the topic, aiming to provide a resource valuable not only to anesthesiologists but also to medical professionals across various specialties.

Muscle Relaxant's Characteristics and Usage After Chemotherapy and Radiotherapy

Depolarizing Muscle Relaxants

Succinylcholine

Succinylcholine (SCC) is a short-acting drug that blocks the action of acetylcholine at the neuromuscular junction.[9] This drug is used as the drug of choice in emergency departments, as it quickly provides optimal conditions for patient intubation.[10]

However, the safety of SCC is controversial according to patients after chemo and radiotherapy. Oral mucositis is a common complication of chemotherapy. Administration of SCC to a patient with inflammation of the oral mucosa and/or esophagus can cause lethal hyperkalemia with a mechanism similar to thermal injury.[11] SCC may also interact with chemotherapeutic agents such as cytarabine, vincristine, or rituximab, causing the patient's muscle paralysis to be prolonged.[12] Radiation treatment causes thermal damage to the muscle cells that leads to hyperkalemia in response to administration of depolarizing neuromuscular blockers such as SCC.[13] Pseudocholinesterase values in cancer patients undergoing radiotherapy are lower than in healthy patients or patients without disease activity.[14] Moreover, in patients not taking radio or chemotherapy, together with the activity of the disease, an increase in the level of pseudocholinesterase can be expected, and as a result, a shortening of the action of SCC.[15]

No correlation was found between the change in pseudocholinesterase levels and the duration and dose of radiotherapy. Therefore, it can be concluded that the pseudocholinesterase values correlate with the activity of the neoplastic disease and not with the reception of radiotherapy.[16]

In patients receiving chemotherapy with cyclophosphamide, pseudocholinesterase activity may be reduced, resulting in a prolonged effect of SCC.[17]

Non-Depolarizing Muscle Relaxants

Amino-Steroids

Pancuronium

Pancuronium (PNC) as a representative of non-depolarizing muscle relaxants is a competitive inhibitor of the postjunctional nicotinic acetylcholine (ACh) receptor. The peak effect of the drug is usually reached within 5 to 10 minutes, and the duration of action may last several hours, ranging from 60 to 180 minutes. In patients with severe electrolyte disturbances, hypokalaemia, hypocalcaemia, hypermagnesaemia, severe fluid and electrolyte disturbances, acid-base

disturbances, as well as in the case of hypoproteinaemia, the effects of PNC bromide may be enhanced and prolonged than normal. In patients with phaeochromocytoma, the administration of PNC bromide may result in significant hypertension. Opioid analgesics, by inhibiting the respiratory center, may contribute to respiratory failure after the use of PNC bromide. PNC relaxant effect is also intensified and prolonged by antibiotics such as: tetracyclines, polymyxin B, lincomycin, clindamycin, capreomycin, colistin and aminoglycoside antibiotics that may be used in patients undergoing radio and chemotherapy.[18] In renal failure, the duration of action of PNC is significantly prolonged because it is excreted by the kidneys. PNC has a greater volume of distribution and slowed elimination, in liver cirrhosis, and which leads to a slower onset and longer duration of action.[13] It was shown that patients with supratentorial tumors have a higher risk of elevation of intracranial pressure while using the PNC in general anaesthesia.[19]

Pipecuronium

Pipecuronium (PPC) is a long-acting, cardio-stable, non-depolarizing muscle relaxant. Various studies have shown its low effect on the cardiovascular system. Chemotherapeutic agents are often eliminated by the kidneys, and this can therefore lead to chemotherapy-induced acute kidney injury (AKI). One of the drugs causing AKI is cisplatin – a drug commonly used in chemotherapy.[20] The main route to elimination of PPC is the excretion of the unchanged molecule in urine.[21,22] However, studies on pigs show that the liver plays a more important role than the kidney in the plasma clearance of PPC.[23] That may suggest similar results in humans. Under chemotherapy, up to 85% of patients develop liver steatosis indicating disturbed lipid metabolism via altered lipoprotein synthesis in the hepatocytes, which can result in excessive levels of PPC in blood and exceeded muscle relaxant effect.[24] PPC also seems very helpful in patients with a risk of higher intraocular or intracranial pressure – like patients with central nervous system (CNS) metastases. It provides greater cardiovascular stability and minimizes the risk of elevating the intracranial pressure during the intubation as well as for the next 30 minutes.[19]

Vecuronium

Vecuronium (VEC) is a muscle relaxant with an intermediate duration of action. VEC remains an alternative drug used for intubation. The drug's main advantages are minimal effects on the cardiovascular system and negligible histamine release to the blood. VEC relaxant effect is also intensified and prolonged by antibiotics such as clindamycin and gentamicin. These drugs may be used during chemo- and radiotherapy.[25] Hyperthermic intraoperative intraperitoneal chemotherapy (HIIC) is an effective method of treatment of intraperitoneal carcinomatosis. This method requires a rise of the core temperature to 39 °C. The studies show that during HIIC the duration time of VEC can be significantly shortened.[26] It was also proven that in renal failure - which is one of the commonly seen problems in cancer patients - the duration of action of VEC was prolonged.[13] VEC is a great choice for breast, non-small-cell lung cancer, and pheochromocytoma (cardiovascular stability and no histamine release), but its usage in gastric cancer is debatable.[19]

Rocuronium

Rocuronium (ROC) is a fast-acting non-depolarizing neuromuscular blocking agent. One of its advantages is the ability to reverse the effect of muscular blockade. ROC should not be used in patients with renal or hepatic dysfunction as it will prolong its effects by delaying elimination.[27] Magnesium sulfate ($MgSO_4$) showed a kidney-protective effect against cisplatin-induced nephrotoxicity (CIN) by regulating renal platinum accumulation both in vitro and in vivo, and the body of clinical data demonstrating the efficacy of this drug in adult cancer patients is increasing.[28] Administration of $MgSO_4$ can affect the time of Rapid Sequence Intubation (RSI). With a 15-minute intravenous infusion of magnesium sulfate 60 mg kg^{-1} before the standard dose of ROC (0.6 mg kg^{-1}), the time to onset of neuromuscular block was reduced by approximately 35%, but recovery was extended by only 25%.[29] ROC is widely used in cancer patients; however, it may be associated with cancer cell invasion, adhesion, and migration, as well as the risk of cancer recurrence especially in breast and gastric cancer patients. ROC does not affect the intraocular or intracranial pressure, so it would be a great choice in cancer patients with central nervous system metastases and cranial hypertension.[19]

In cases when faster muscle blockade reverse is needed we can use Sugammadex. It can reverse the effects of amino-steroid neuromuscular blockers such as PNC, PPC, ROC, and VEC, which action could sometimes be prolonged in cancer patients than in healthy population. Sugammadex is also thought to promote recovery after surgery in oncological patients.[19]

Benzylisoquinolines

Atracurium

Atracurium (ATC) is a drug from a group of moderately long-acting drugs. It is independent from pseudocholinesterase activity due to removal by Hofmann elimination which may make it a good choice for patients with liver or kidney dysfunction.[30,31] Neuromuscular blockade is shortened during hyperthermic intraperitoneal chemotherapy (HIPEC). The shorter duration of action of ATC is due to the increased clearance of ATC during hyperthermia.[32] ATC promotes astroglial differentiation, depletes glioblastoma stem cells and decreases the cell proliferation of hepatocellular carcinoma. Due to these effects, its use in general anesthesia may be considered in patients with these two types of tumors.[19,33]

Cisatracurium

Cisatracurium (CSC) is characterized by an intermediate long duration of action and independence from pseudocholinesterase due to removal by Hofmann elimination, which may make it a good choice for patients with liver or kidney dysfunction. CSC shows about four times stronger effect, than atracurium, maintaining its minimal effect on the cardiovascular system.[31] Prolonged onset of action of CSC shortened duration of action and faster recovery have been observed in patients undergoing neoadjuvant chemotherapy.[34] In addition, patients require additional CSC injections to maintain the neuromuscular blockade effect.[35] In the review by Chen et al, we can find information about the effective inhibition of the proliferation and spread of cancer cells by CSC and the essence of its use in cancer patients. CSC acts through many molecular pathways such as induction of apoptosis in gastric cells, decreasing the proliferation, migration, and invasion of breast cancer cells, and inhibition of colorectal cancer progression, by altering the p53-dependent apoptotic pathway.[19]

Mivacurium

Mivacurium (MVC) is a non-depolarizing muscle relaxant with the shortest duration of action. It is metabolized by pseudocholinesterase.[20] Deficiency or abnormal plasma levels of cholinesterase can result in a significant prolongation of the duration of action of both succinylcholine and mivacurium.[36] Information about MVC and oncological patients is still very limited.

The summary of the main differences of function found in literature in chosen myorelaxants in the course of radio and chemotherapy in patients is shown in Table 1.

Table 1 The Summary of Muscle Relaxants Function Changes in Patients Under or After Radio and Chemotherapy

Substance	Function Changes in Radio-Chemotherapy	Reference
Succinylcholine (SCC)	• SCC-induced hyperkalemia in patients under radiotherapy with thermal damage of cells • Prolongation of the duration of action of SCC in patients under chemotherapy.	[13,14]
Pancuronium (PNC)	• Enhanced and prolonged duration of action in electrolytes and acid-base balance disturbances, and renal failure	[13,18]
Pipecuronium (PPC)	• Excessive levels of PPC in blood and exceeded muscle relaxant effect in patients with renal or hepatic failure	[24]
Vecuronium (VEC)	• During HIIC the duration time of VEC can be significantly shortened • The duration of action of VEC was prolonged in renal failure	[13,26]
Rocuronium (ROC)	• Prolonged duration of action in patients under neoadjuvant chemotherapy • Poor effect of intraoperative rocuronium muscle relaxation in patients after chemotherapy	[37,38]
Atracurium (ATC)	• Shortening of action during HIPEC	[32]
Cisatracurium (CSC)	• Prolonged onset of action of CSC, shortened duration of action, and faster recovery in patients under neoadjuvant chemotherapy • Patients require additional CSC injections to maintain the neuromuscular blockade effect	[34,35]
Mivacurium (MVC)	• Prolongation of the duration of action of MVC in chemotherapy patients	[36]

Abbreviations: HIIC, hyperthermic intraoperative intraperitoneal chemotherapy; HIPEC, hyperthermic intraperitoneal chemotherapy.

Conclusions

Anesthesiologists need to be vigilant regarding cancer patients undergoing chemotherapy and radiotherapy, and the impact of its side effects on various organ systems. Ensuring optimal treatment for cancer patients necessitates essential collaboration between anesthesiologists, oncologists, and surgeons. The monitoring of the neuromuscular blockade is a very important part of the effective muscle relaxation of the patients in the operative room. Our work describes the information found on chosen muscle relaxants in context to their characteristic changes in cancer patients. The amount of available literature specifically on changes in the action of a given drug in a patient after chemotherapy or radiotherapy is still scant. Different myorelaxants behave differently in oncological patients. Pseudocholinesterase activity is remarkably decreased in patients after chemotherapy and radiotherapy, and it contributes to the elongation of the time of SCC and MVC action. Meanwhile, CSC action in patients undergoing chemotherapy had prolonged onset and was significantly shortened. The duration of action of all muscle relaxants metabolized by kidneys is prolonged in renal failure. The authors' opinions are still divided, as in the case of rocuronium, where some authors report its prolonged effect, while others report a completely different effect and a very weakened effect in patients after neoadjuvant chemotherapy. Interaction between radio and chemotherapy in cancer patients and muscle relaxing agents has not yet been thoroughly investigated and the amount of reports on this subject is still limited. Depending on their mechanism of action, muscle relaxants behave differently in patients receiving cancer treatment. Additional investigation is needed to explore optimal strategies that can improve the management of anesthesiologic teams in cancer patients.

Abbreviations

Ach, Acetylcholine; ATC, Atracurium; CIN, Cisplatin-induced nephrotoxicity; CNS, Central nervous system; CSC, Cisatracurium; HIIC, Hyperthermic intraoperative intraperitoneal chemotherapy; HIPEC, Hyperthermic intraperitoneal chemotherapy; MgSO4, Magnesium sulfate; MVC, Mivacurium; PNC, Pancuronium; PPC, Pipecuronium; ROC, Rocuronium; RSI, Rapid Sequence Intubation, SCC, Succinylcholine; VEC, Vecuronium.

Disclosure

The authors report no conflicts of interest in this work.

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