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REVIEW

The Use of Muscle Relaxants in Pregnancy and Puerperium Period

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Introduction: Anaesthetising a pregnant woman and during the postpartum period is challenging for most anaesthetists. There are many factors involved, including all the physiological changes that occur in the body of such a woman. Particular attention should be paid to muscle relaxants.

Aim: The purpose of this article is to present the use of muscle relaxants in pregnancy and puerperium period.

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

Conclusion: In our experience and from a broad review of the medical literature, a great deal of caution should be exercised when using muscle relaxants during the anaesthesia of pregnant or postpartum patients. The pharmacodynamic and pharmacokinetic differences in the action of this group of drugs during this period should be known.

Keywords: muscle relaxant, pregnancy, puerperium period, anaesthesia

Introduction

Changes in maternal physiology can affect both pharmacokinetics and pharmacodynamics of muscle relaxant drugs. These changes vary depending on the type of drug used.

The increased plasma volume during pregnancy by up to 45% results in decreased plasma protein concentration, which is relevant for water-soluble drugs, such as Rocuronium or Pancuronium, which belong to amino-steroid non-depolarising muscle relaxants. The state of decreased albumin–globulin ratio results in higher concentration of free drugs in blood. Liver and kidneys play a major role in excretion and metabolism of drugs. During pregnancy glomerular filtration rate increases by 50–60% with no change in hepatic blood flow. Alteration of both of these organs during pregnancy results in change of drug concentration in blood. Moreover, an increase in cardiac output is observed, which results in faster onset of muscle relaxant drugs.[2]

General anaesthesia is not commonly performed in pregnant women or during the puerperium period. Usually, regional anaesthesia is the method of choice due to decreased risk of maternal mortality. However, the indications for general anaesthesia include among others stopping the eclamptic seizure and caesarian section.[28] Magnesium sulfate used in the prevention and treatment of pre-eclampsia are affecting the duration of action of nondepolarizing muscle relaxants. The differences in metabolism of muscle relaxants combined with major physiological changes during pregnancy results in various changes in the activity of drugs.[27]

Both non-depolarizing and depolarizing muscle relaxants pass through the placenta poorly. The main reason for this is the lipophilicity of these drugs, their ionization, and strong protein binding. These molecular features will ensure that no muscle relaxant will pass freely across the placenta.

Material and Methods

The work is based on the available literature and the author's experience. The aim of this study was to review the use of muscle relaxants in pregnancy and puerperium period. The search process resulted in the detection of relevant articles

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using valid keywords on electronic databases, including Embase, PubMed, Scopus, Web of Science, and Cochrane Library. Subsequently, 31 articles published from 1979 to 2022 were identified as eligible for our review. The search terms "muscle relaxants" and "pregnancy" or "puerperium" were also used. Initially, a list of titles and abstracts of all the articles on the searched databases were provided by two researchers and were reviewed separately to detect and select relevant titles. Subsequently, the related articles were independently included in the research process. We also paid special attention to the clinical approach of the topic, so that this article will be useful not only for anesthesiologists but also for doctors from a variety of specialties. Hence, while the topic is not new, our holistic approach make it a useful resource for many doctors. We have paid considerable attention to both, the latest publications and the fundamentals of anesthesiology.

Results and Discussion

Muscle Relaxants Characteristics in Pregnancy and the Puerperium Period

Depolarizing Muscle Relaxants

Succinylcholine is the only currently used depolarizing muscle relaxant agent in pregnancy and puerperium period. The effectiveness and the time of neuromuscular blockade depend on the activity of pseudocholinesterase, which changes during pregnancy and the puerperium period. During physiological pregnancy serum levels of pseudocholinesterase are decreased by up to 30%. There is a sudden drop in plasma pseudocholinesterase levels during the first trimester of pregnancy. This condition remains throughout pregnancy and until about the 7th day after giving birth. During the 2nd trimester, a slight increase in pseudocholinesterase levels is observed, which continues until the beginning of the 3rd trimester.[3] The normal levels of pseudocholinesterase are returning 6 weeks after labor. After receiving normal doses of succinylcholine, patients with physiological pregnancy should not be presenting prolonged apnea.[4]

None Depolarizing Muscle Relaxants

Amino-Steroids

Pancuronium. Due to this agent's long activity, it is not currently used in pregnancy. Four-milligram dose usually does not effect maternal blood pressure and cardiorespiratory activity of the fetus. Moreover, pH and pCO2 levels go back to normal state up to 30 minutes after delivery. Comparing the Apgar score, the overall score was lower in patients after pancuronium dosage. Moreover, the heart rate and ventilation of newborns is believed to stay in the normal range even after 4mg pancuronium dose.[6]

Pipecuronium. A muscle relaxant with a long duration of action. Pipecuronium is used in the Caesarian section as an alternative to succinylcholine, because of its poor placental transfer and inconsiderable cardiovascular effect. It also shows no effect on newborns.[7] Moreover intramuscular fetal injection of pipecuronium in 0.2 mg/kg dose results in a safe and temporary neuromuscular blockade and allows safe intra-uterine surgeries without the need for extra maternal anesthesia.[8]

Vecuronium. A muscle relaxant with an intermediate duration of action. Vecuronium remains an alternative drug used for intubation. The drugs' main advantages are minimal cardiovascular system effects and negligible histamine release. Vecuronium also shows poor placenta transfer, which helps maintaining maternal sedation without concern about fetal muscle relaxation.[9] Compared with non-pregnant women vecuronium duration of action is lengthened during pregnancy and in the puerperium period.[22,23] Because of the minimal cardiovascular effect and poor placenta transfer vecuronium remains a third alternative to use for intubation in women requiring Caesarian section.[9]

Rocuronium. Rocuronium is currently the most commonly used skeletal muscle relaxant during pregnancy and puerperium period. The drug is characterized by a quick onset of action, which is about 25% shorter during pregnancy compared to non-pregnant women[12] intermediate duration of action which, however, is prolonged in pregnant women.[10] Moreover, rocuronium is not associated with the risk of malignant hyperthermia, hyperkalemia, CN X blockade, and does not increase the intracranial or intraocular pressure.[11] Rocuronium effect can be reversed with sugammadex, which makes this drug a great alternative in sedation during pregnancy and puerperium period. Moreover, Rocuronium is used in ECT during pregnancy and puerperium period as an alternative for Succinylcholine due to the safety of the drug and its predictability when used in a pregnant patient. Moreover, succinylcholine does not have any reversing agent. Some

studies show that Rocuronium usage in first-trimester pregnant patients may cause breathing problems in newborns or even be fatal for them.[10] Anesthesia with rocuronium provides good conditions for physiological delivery. This drug enables patients to give birth more easily. In addition, the time between making the incision and removing the baby is shortened. Rocuronium provides a fairly long duration of action after its administration. Even with prolonged labor, muscle relaxation is maintained, as in the case of using suxamethonium to anesthetize physiological labor.[11] Previous studies indicate that rocuronium 1 mg/kg and suxamethonium 1 mg/kg is a comparable choice of muscle relaxants in terms of obstetric airway management and in the effect on the neonate at Apgar (5 min) for general anesthesia for emergency cesarean sections. Rocuronium can cross the placenta to a lesser degree, as opposed to suxamethonium, and maybe in some cases affect the Apgar score at 1 min.[11,29]

Benzylisoquinolines

Atracurium. Atracurium is a drug from a group of moderately long-acting drugs. It is independent of pseudocholinesterase activity due to removal by Hofmann elimination.[5] After the use of atracurium as a muscle relaxant in pregnant women, no health problems were observed in their newborns. The muscle blockade caused by Atracurium can be reversed easily by administering sugammadex. Atracurium is a useful drug in pregnant patients undergoing Caesarian section due to the low degree of placenta transfer.[13] The rate of transition of non-depolarizing muscle relaxants may be altered due to the patient's illness. In this case, the increased permeability of drugs through the placenta should be taken into account. Atracurium is characterized by a lower transfer rate than other non-depolarizing muscle relaxants.[14] Also, Atracurium does not affect mean arterial pressure, but after its administration, the drug may cause a significant drop in heart rate in pregnant patients.[13]

Cisatracurium. Cisatracurium is characterized by an intermediate long duration of action and independence from pseudocholinesterase due to removal by Hofmann elimination.[15] Cisatracurium shows about four times stronger effect than atracurium, remaining its minimal effect on the cardiovascular system. The time of neuromuscular blockade is shorter in pregnant patients compared to non-pregnant patients. This state is caused by physiological changes and organ-independent Hofmann elimination. The physiological changes that may affect cisatracurium elimination are increased cardiac output and decreased protein binding in the perinatal period. This makes Cisatracurium characterized by a rapid onset of action and short duration of action, which is a desirable phenomenon in pregnant women.[1,5,16]

Mivacurium. Mivacurium is a non-depolarizing muscle relaxant with the shortest duration of action. It is metabolized by pseudocholinesterase.[4] Due to the elimination of mivacurium by pseudocholinesterase, its activity is reduced during pregnancy and in the perinatal period.[4] This fact is caused by a decrease in pseudocholinesterase activity in these periods. Compared to atracurium and vecuronium, mivacurium has a time of action shorter by about half. Due to its duration of action, mivacurium is used in patients taking magnesium as the prevention of eclampsia. Mivacurium has also been used as a muscle relaxant used in Caesarean section.[5,17] In postpartum patients, the neuromuscular blockade time is extended by approximately 3 minutes. Usually, the prolongation of neuromuscular blockade in postpartum patients is not clinically relevant, but the patient's plasma cholinesterase should be tested.[18]

Muscle Relaxants Reversal Agents

Neostigmine

Neostigmine is often used to reverse muscle relaxation during general anaesthesia for caesarean section. This drug has been shown to have no effect on the duration of labor and has no neurotoxic effects on the spinal cord and on the blood flow in the spinal cord. Due to its polar structure, neostigmine crosses the placenta to a limited extent. If neostigmine is administered to a pregnant woman, fetal bradycardia may occur.[22] Moreover, the use of neostigmine under epidural anesthesia allows reducing the amount of local anesthetics administered in an intradural block. Neostigmine administered as an adjuvant under local anesthesia allows less frequent use of opioids and anesthetics.[19] Due to the limited efficacy of neostigmine alone, it is recommended to use it with sufentanil or clonidine. In combination with those drugs, neostigmine provides analgesia and does not cause any side effects.[21] Neostigmine administered epidurally or neuraxial shows no side effects both in parturients and fetus. Intrathecal use of neostigmine may cause different side effects that are dependent on the dose of a drug. Administration of <50ug can cause nausea, vomiting, and leg

weakness, which are the most frequent side effects of neostigmine administered intrathecally. Doses >200ug might cause contractions of the uterus, hallucinations, and hypertension. Because of the numerous side effects, intrathecal neostigmine is preferred in lower doses in order to cause labor analgesia. The caudal route of administration shows efficient analgesia, though it may cause vomiting in parturients. Also, neostigmine administered intraarticularly causes effective pain relief in labor.[20]

Sugammadex

Sugammadex provides a strong reversal of neuromuscular blockade caused by aminosteroid agents. In addition, its effectiveness and lower side effects compared to neostigmine make it an alternative for pregnant women undergoing non-obstetric surgery. Sugammadex interacts with progesterone, which may reduce its concentration in pregnant women, which poses a risk of maintaining pregnancy, especially in the early stages. The latest study suggests poor placenta transfer of sugammadex.[22] Sugammadex has a very strong affinity for the aminosteroid muscle relaxants. Due to its quick onset of action, sugammadex is often used to reverse neuromuscular blockade, especially in late pregnancy due to the binding of progesterone, the physiological concentration of which is essential to maintain early pregnancy.[23] Sugammadex has been reported to cause neuronal apoptosis in fetuses when administered in pregnant women.[24] Despite the lack of research, it is believed that due to its polarity and particle size, sugammadex is poorly transferred into breast milk and poorly absorbed by the newborn.[25]

Limitations

This review has potential limitations. The most significant of these is that, this is not a systematic review. Therefore, more research is needed on this topic.

Conclusion

Approximately 2% of pregnant women require surgical treatment for non-obstetric reasons, most commonly due to appendicitis, cholecystitis, cancer or trauma. Surgical procedures during pregnancy are associated with an increased risk of preterm delivery or miscarriage. It is recommended that elective surgeries be carried out after the end of pregnancy and the puerperium. If they are necessary during pregnancy, it seems optimal to perform them in the second trimester of pregnancy, which is associated with the lowest risk of miscarriage and preterm birth. However, urgent surgery should not be postponed, regardless of the trimester of pregnancy.

Non-depolarising muscle relaxants are an interesting group from the point of view of safety in pregnancy. The FDA classifies them in cat C. It should be emphasised that the fact of poor permeability of a drug into the fetal circulation does not constitute convincing evidence of the absence of harm in terms of generating malformations. These two facts must be clearly distinguished and an almost imposing simplification must be avoided: it does not penetrate the foetal circulation and therefore does not cause malformations. Relaxants are used during RSI. In the UK, 90% of obstetric anaesthetists still use succinylcholine (at a dose of 1–1.5 mg/kg) for caesarean sections. Its effect in pregnancy may be prolonged due to a reduction (up to >25%) in plasma cholinesterase activity. Alternatively, rocuronium can be used at a dose appropriate for RSI (1 mg/kg) to achieve readiness for intubation as soon as possible. The use of rocuronium and sugammadex during caesarean section is discussed as an alternative drug for difficult intubation - this offers the possibility of reversing the block in less time than the action of succinylcholine.

The Society for Obstetric Anesthesia and Perinatology does not recommend the use of sugammadex in pregnant women unless there is an absolute benefit due to the unforeseen need to reverse the relaxant (“can”t intubate, cannot oxygenate’ situation) or inadequate block reversal with cholinesterase inhibitors. When using a cholinesterase inhibitor and atropine, it should be borne in mind that atropine passes through the placenta and, given in high doses, can cause fetal tachycardia and unresponsiveness in the OCT recording. The use of magnesium sulphate may prolong the effect of muscle relaxants.

Disclosure

The authors report no conflicts of interest in this work.

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