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Navigating Anesthesia: Muscle Relaxants and Reversal Agents in Patients with Renal Impairment

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This comprehensive review explores the interaction between neuromuscular blocking agents, reversal agents, and renal function, focusing on various drugs commonly used in anesthesia and their effects on kidney health. Succinylcholine, commonly used for anesthesia induction, can trigger elevated potassium levels in patients with specific medical conditions, leading to serious cardiac complications. While studies suggest the use of succinylcholine in patients with renal failure is safe, cases of postoperative hyperkalemia warrant further investigation. Some agents, such as atracurium and mivacurium, are minimally affected by impaired kidney function, whereas others, such as cisatracurium and rocuronium, can have altered clearance, necessitating dose adjustments in patients with renal failure. The reversal agents neostigmine and sugammadex affect renal markers, while cystatin C levels remain relatively stable with sugammadex use, indicating its milder impact on glomerular function, compared with neostigmine. Notably, the combination of rocuronium and sugammadex in rat studies shows potential nephrotoxic effects, cautioning against the simultaneous use of these agents. In conclusion, understanding the interplay between neuromuscular blocking agents and renal function is crucial for optimizing patient care during anesthesia. While some agents can be used safely in patients with renal failure, others can require careful dosing and monitoring. Further research is needed to comprehensively assess the long-term impact of these agents on kidney health, especially in high-risk patient populations. This article aims to review the use of muscle relaxants and reversal for anesthesia in patients with impaired renal function.

Keywords: Neuromuscular Blockade • Neuromuscular Blocking Agents • Renal Insufficiency • Renal Insufficiency, Chronic • Review

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Introduction

Skeletal muscle relaxants are drugs that have found wide application in anesthesiology as compounds that facilitate the preparation of patients for surgery, support mechanical ventilation, ease the process of intubation, and reduce the risk of trauma during the procedure. The neuromuscular blockade they induce makes muscles unresponsive to further impulses. Reversals, on the other hand, are drugs that counteract the effects of muscle relaxants. The ability to use them is very important because they allow us to reverse the neuromuscular blockade [1].

In the domain of anesthesiology, the administration of pharmacological agents for inducing and maintaining anesthesia has undergone remarkable advancement, enabling the execution of intricate surgical procedures with enhanced patient comfort and safety. Amid this progress, the emergence of anesthesia reversal agents, as indispensable components in the anesthetic continuum, has markedly expedited patient recovery by swiftly countering the effects of administered anesthetics. While these agents have demonstrated undeniable benefits in clinical practice, a growing body of research and clinical observations has underscored the need for a meticulous evaluation of their potential effect on renal function. The kidneys, central to maintaining fluid homeostasis, electrolyte equilibrium, and waste elimination, represent a vital organ system with intricate physiological interdependencies. Any disruptions in renal function can cascade into systemic imbalances, jeopardizing not only immediate post-anesthetic recovery but also the long-term renal health of patients. Water solubility is a critical factor in drug pharmacokinetics, affecting the dissolution, absorption, distribution, metabolism, and excretion of a compound in the body. Reversal agents with higher water solubility generally exhibit faster onset of action and efficient elimination from the body. Conversely, poorly water-soluble agents can have delayed effects and prolonged accumulation in tissues, which could increase the risk of adverse events. As a result, the interaction between anesthesia reversal agents and renal physiology merits comprehensive scrutiny to elucidate potential nephrotoxic implications [1,2].

The function of the kidneys can influence how reversal agents act in the body. The kidneys play a crucial role in filtering and excreting drugs and their metabolites from the bloodstream. If the kidneys are not functioning properly, they may not effectively clear the reversal agent or the drugs it is countering from the body. This can lead to altered drug levels, potential accumulation, and changes in the effectiveness or adverse effects of both the reversal agent and the drugs it is interacting with. When drugs and their metabolites are not effectively cleared from the body due to kidney dysfunction, they can accumulate in the bloodstream. This can lead to higher-than-intended drug levels, which might result in increased adverse effects or even toxicity. Additionally, the altered drug levels can affect the overall pharmacodynamics (how the drug affects the body) and pharmacokinetics (how the body processes the drug) of the reversal agent and the drugs it is countering. Therefore, kidney function can affect the metabolism and elimination of the reversal agent and the drugs involved, affecting their overall actions and effects [3].

In this article, we aim to review the use of muscle relaxants and reversal for anesthesia in patients with impaired renal function.

Neuromuscular Blocking Agents

Drugs causing neuromuscular blockade find wide application in anesthesiology. Depending on the mechanism by which they induce blockage of conduction, they are divided into non-depolarizing (this group includes drugs such as atracurium, pipecuronium, mivacurium, rocuronium, and vecuronium), which act as competitive antagonists of the nicotinic receptor, and depolarizing (such as succinylcholine), which, by acting similarly to acetylcholine, bind to the receptor and induce depolarization, followed by a sustained block. Non-depolarizing neuromuscular blocking agents can be classified based on their structure into steroid, benzylisoquinolinium, and asymmetrical mixed-onium chlorofumarate. Several aspects, such as sex, age, weight, body temperature, concurrently administered medications, liver and kidney dysfunction, electrolyte disturbances, and acid-base balance disorders, can influence the action of neuromuscular blocking agents, and consequently, the strength and duration of the induced blockade. Neuromuscular blocking agents are widely used in anesthesiology to aid in safe intubation, reduce the risk of trauma, prepare patients for surgery, and support mechanical ventilation [1,4].

Renal Function Assessment

Assessment of kidney function is an important aspect of clinical practice. As previously mentioned, the kidneys play a crucial role in maintaining homeostasis in the body. In cases of impaired kidney function, the elimination of drugs from the body can be slowed down. Consequently, this can lead to the accumulation of the drug in the body and an enhancement of its effects. Some drugs and their metabolites, in increased concentrations, can lead to further kidney damage.

We can assess kidney function using several parameters. Generally, the best parameter for evaluating kidney function is the assessment of glomerular filtration rate (GFR). This test shows the rate at which substances are filtered by the renal glomeruli; that means how quickly they are removed. The test result is given in mL/min/1.73 m^2. Normally, the GFR value should be ≥90 mL/min/1.73 m^2. To measure GFR, we are

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using exogenous or endogenous substances that should have such features as: (1) they do not undergo metabolic transformations in the body; (2) they are freely and completely filtered in the renal glomeruli; (3) they are not reabsorbed from the filtrate at any segment of the nephron, nor are they secreted into it; and (4) they are produced at a constant rate (applies exclusively to endogenous substances).

The reference method for evaluating GFR is the filtration assessment using inulin. Other exogenous substances that can be used for the test include iohexol and radioisotopes, such as chromium-51 ethylene-diamine-tetra-acetic acid and technetium-99-labeled diethylene-triamine-pentaacetate. To count it, the following equation is used: GFR=[urineX (mg/mL)×urine flow (mL/min)]/[plasmaX (mg/mL)], where X is a substance that is completely excreted [5].

Another way to calculate GFR is by using an endogenous marker such as creatinine. In this case, its clearance (CrCl) is used. The formula C=(U×V)/P, where C=clearance, U=urinary concentration, V=urinary flow rate (volume/time, ie, mL/min), and P=plasma concentration, is used in this case. In creatinine clearance, the previously mentioned features 1 and 2 are met, 3 is only partially met, while 4 is not met. In case of significant kidney damage due to tubular secretion, creatinine can overestimate GFR by approximately 10% to 20% [5,6].

Assessing renal clearance using exogenous markers is difficult, and CrCl is used in few cases. Therefore, in clinical practice, the estimated glomerular filtration rate (eGFR), calculated based on equations that consider endogenous filtration markers, is more commonly used. The most frequently used of these markers is creatinine [5,7]. The use of creatinine as a marker is imperfect since its concentration is influenced by factors such as age, sex, race, muscle mass, existing chronic or acute diseases, medications, and diet [8]. Another endogenous marker that can be used is cystatin C. Its advantage over creatinine is that its concentration is not affected by age, muscle mass, or diet. Some reports suggest it is a more reliable marker for assessing eGFR, especially in early renal impairment, than creatinine [5].

Equations such as the Modified Diet in Renal Disease equation, which considers creatinine concentration, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations, such as the CKD-EPI creatinine equation, CKD-EPI creatinine-cystatin equation, and CKD-EPI cystatin C equation, can be used to assess eGFR [5]. In children, the Schwartz formula is used, which includes the serum creatinine level and child's height, to estimate GFR [6].

Recently, new biomarkers, such as β2-microglobulin and retinol-binding protein, have become useful in the assessment of kidney function [5].

Impaired Renal Function

Conditions affecting the kidneys can be considered chronic or acute depending on their duration. When kidney function is impaired (there is presence of kidney damage or an eGFR less than 60 mL/min per 1.73 m^2) for 3 months or more, we refer to it as chronic kidney disease (CKD). However, when the deterioration of function occurs over a shorter period, we refer to it as acute kidney diseases and disorders (AKD) or acute kidney injury (AKI). The term AKD is relatively new, having been introduced in recent years. The concept behind introducing the term AKD was the presence of patients who did not meet the criteria for AKI and CKD but still required increased attention and medical monitoring. AKD has been defined by abnormalities of kidney function and/or structure with health implications lasting less than 3 months and includes AKI, which is defined as a subset of AKD, with the onset of development within 7 days due to various causes [9-12].

According to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, the following criteria must be met to diagnose CKD. Either of the following must be present for a minimum of 3 months:

- markers of kidney damage (1 or more):
  - albuminuria (albumin to creatinine ratio (ACR) ≥30 mg/g [≥3 mg/mmol])
  - urine sediment abnormalities
  - persistent hematuria
  - electrolyte and other abnormalities due to tubular disorders
  - abnormalities detected by histology
  - structural abnormalities detected by imaging
  - history of kidney transplantation
- decreased GFR
  - GFR <60 mL/min per 1.73 m^2.

The classification of CKD is based on 2 parameters: decreased GFR and albuminuria. **Table 1**, which is adapted from the KDIGO 2024 Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease, presents the stages of CKD based on GFR [10].

According to the KDIGO guidelines, AKI is defined as any of the following:

- increase in serum creatinine level by ≥0.3 mg/dL (≥26.5 lmol/L) within 48 h; or
- increase in serum creatinine level to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- urine volume <0.5 mL/kg/h for 6 h.

AKI can be further divided into 3 stages depending on the increase in serum creatinine concentration or the decrease in urine output. In 2012, KDIGO introduced an operational

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Table 1. Stages of chronic kidney disease based on glomerular filtration rate (GFR).

GFR Category	GFR (mL/min per 1.73 m²)	Terms
G1	≥90	High or normal
G2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

definition of AKD in their guidelines on AKI. To diagnose AKD, the following criteria should be met:

- functional criteria
  - occurrence of AKI, or
  - GFR < 60 mL/min per 1.73 m^2 for <3 months, or
  - decrease in GFR by ≥35% or
  - increase in serum creatinine level by >50% for <3 months, or
- structural criteria
  - structural kidney damage <3 months (albuminuria, hematuria, or pyuria are most common) [9,11].

Succinylcholine Characteristics

Succinylcholine, also known as suxamethonium, is a neuromuscular blocking agent commonly used in anesthesia. It is primarily metabolized by the enzyme pseudocholinesterase (also known as plasma cholinesterase or butyrylcholinesterase) in the bloodstream, rather than in the kidneys. Regarding renal involvement, the kidneys do play a role in the elimination of succinylcholine and its metabolites from the body. After the breakdown of succinylcholine by pseudocholinesterase, the resulting choline is primarily excreted in the urine. Additionally, some succinylmonocholine and other metabolites can be excreted by the kidneys [13].

Succinylcholine Impact on the Levels of Potassium in Blood

When succinylcholine is given to healthy individuals, it causes a slight and short-lived increase in the levels of potassium in the blood. This increase, which is typically from 0.5 to 1.0 mEq/L, occurs within 3 to 5 min after administering succinylcholine through an intravenous injection and lasts for less than 10 to 15 min. The reason for this rise in potassium level is believed to be the release of potassium from cells, due to depolarization specifically at the neuromuscular junction, which is the connection between nerves and muscles. However, in certain medical conditions, such as trauma, burns, infections, and certain neuromuscular disorders, including spinal cord injury, upper motor lesions, structural brain damage, peripheral nerve injury, peripheral neuropathy, Parkinson disease, tetanus, and muscular dystrophy, there is an exaggerated increase in serum potassium levels when succinylcholine is administered. This heightened response can lead to serious complications, including cardiac dysrhythmias (abnormal heart rhythms) and potentially even cardiac arrest. The reason for this exaggerated increase in serum potassium in these conditions is believed to be the presence of an excessive number of acetylcholine receptors beyond the usual neuromuscular junction (known as extra-junctional receptors). Due to this proliferation of receptors, the movement of potassium is not restricted to the neuromuscular junction as it should be in healthy individuals. Consequently, when succinylcholine induces depolarization, there is an excessive release of potassium from cells, leading to dangerously high potassium levels in the bloodstream [13].

Use of Succinylcholine in Patients with Renal Impairment

The use of succinylcholine in patients with renal failure has raised concerns about potentially triggering a severe increase in potassium levels (hyperkalemia), which could lead to adverse cardiac effects. However, previous studies, including case reports, case series, and controlled studies, have provided evidence supporting the safety of using succinylcholine in patients with renal failure, as long as certain conditions are met. The consensus from these studies is that succinylcholine can be considered safe in patients with renal failure, provided that they do not have associated neuropathy (nerve damage) or preoperative hyperkalemia (elevated potassium levels before surgery). Additionally, it is essential to avoid administering repeated doses of succinylcholine to these patients. Despite the previously existing evidence, the institution of Thapa and Brull, who, in 2000, conducted a review of the topic of succinylcholine-induced hyperkalemia in patients with renal failure, observed cases of postoperative hyperkalemia in patients with renal failure who were given succinylcholine during surgery. These patients had normal potassium levels before the

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surgery, but potassium levels during surgery were not measured, making it challenging to pinpoint the exact cause of hyperkalemia in these cases [13].

In the literature, a case of a 30-year-old patient who developed rhabdomyolysis and acute renal failure after undergoing a minor operation under general anesthesia was reported. During the surgery, succinylcholine was given as a muscle relaxant, and it is suspected that the fasciculations (involuntary muscle contractions) that occurred immediately after the injection of succinylcholine may have contributed to the development of rhabdomyolysis. In simpler terms, after receiving succinylcholine during surgery, this patient experienced muscle twitches, and it is believed that these twitches may have triggered the condition known as rhabdomyolysis, which involves the breakdown of muscle tissue. As a consequence of rhabdomyolysis, the patient's kidneys were affected, leading to acute renal failure [14].

Benzylisoquinoline Neuromuscular Blocking Agents

Pancuronium, doxacurium, and pipecuronium should not be administered in patients with kidney failure, because they undergo renal excretion, whereas atracurium and cisatracurium are good alternatives in patients with kidney or liver diseases, because they are metabolized by a special degradation sequence called the Hoffman reaction [15].

Atracurium and Its Use in Reduced Kidney Function

Atracurium undergoes metabolism primarily in the liver, with minimal involvement of the kidneys. This means that the drug is not extensively metabolized or eliminated by the kidneys. Therefore, patients with impaired kidney function do not need dose adjustments or alterations in the administration of atracurium. However, it is important to monitor renal function in these patients to ensure the drug is being cleared appropriately [4].

In 2020, Ciobotaru et al conducted a study in 2 hospitals involving 905 patients who were divided into 2 groups based on the muscle relaxant used during induction: succinylcholine or atracurium. The study aimed to examine and compare the occurrence of allergic reactions between succinylcholine and atracurium. All other medications administered during induction were identical in terms of the order and dosage relative to the patient's weight. In other words, the only difference between the 2 groups was the type of muscle relaxant used. It was established that atracurium had a longer acting time than did succinylcholine, but it carried a lower risk of causing elevated potassium levels in the blood. This is particularly crucial for patients with cardiac disorders or kidney diseases [16].

Mivacurium and Its Use in Reduced Kidney Function

Mivacurium is primarily metabolized in the liver through ester hydrolysis by plasma cholinesterase. The drug undergoes minimal renal metabolism, and the metabolites are mainly excreted in the urine [4]. Therefore, patients with impaired kidney function can experience delayed clearance of mivacurium and its metabolites, leading to prolonged drug effects. Dose adjustments can be necessary in these patients to avoid excessive muscle relaxation and potential adverse effects. Monitoring renal function and adjusting the dosage accordingly is recommended in patients with renal impairment.

Blobner et al conducted a study in which the effect of renal function on the pharmacodynamics of mivacurium was investigated. Sixty patients were divided into 3 groups based on their creatinine clearance levels: a control group with creatinine clearance greater than 50 mL/min; a (preterminal renal failure group with creatinine clearance between 50 and 20 mL/min; and a terminal renal failure group with creatinine clearance less than 20 mL/min. To assess neuromuscular transmission, electromyography was used to monitor the train-of-four response in the hypothenar muscle, stimulated by the ulnar nerve. An initial bolus of mivacurium was given, followed by a continuous infusion to maintain the neuromuscular blockade at 5% to 4% of baseline (T1 value). Interestingly, it was found that the dose of mivacurium required to achieve 95% neuromuscular block was comparable across patients with normal renal function and those with different degrees of renal impairment. However, when it came to the recovery from neuromuscular block after stopping the mivacurium infusion, a significant delay in patients with preterminal renal impairment was observed. This means that patients with impaired renal function took longer to regain their neuromuscular function after the administration of mivacurium. Furthermore, a strong association between the pharmacodynamics of mivacurium and the activity of pseudocholinesterase, an enzyme responsible for breaking down mivacurium in the body, was established. However, there was no similar correlation with creatinine clearance, suggesting that pseudocholinesterase activity may play a more critical role in determining the drug's effects than the level of creatinine clearance of patients. In summary, this study demonstrated that the dose requirement for mivacurium to achieve neuromuscular block is not significantly influenced by renal function, but that impaired renal function, particularly in preterminal renal failure, can lead to prolonged recovery from the neuromuscular blockade. Additionally, the pharmacodynamics of mivacurium strongly

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relate to pseudocholinesterase activity rather than creatinine clearance levels in these patients [17].

Prolonged neuromuscular block in patients with end-stage renal disease after infusion of mivacurium has been also established, in a study conducted by Mangar et al [18].

Cisatracurium and Its Use in Reduced Kidney Function

Cisatracurium is primarily metabolized in the liver through Hofmann elimination, a non-enzymatic process. Therefore, it does not undergo significant renal metabolism. After metabolism, the metabolites are excreted primarily through the urine. This is important to consider in patients with renal impairment, as the clearance of cisatracurium can be reduced, leading to prolonged effects of the drug [19].

Rocuronium-Sugammadex vs Cisatracurium-Neostigmine: Effect on Kidney Recovery after Kidney Transplantation

The objective of a retrospective case-control study conducted by Vargas et al was to examine the effects of rocuronium-sugammadex versus cisatracurium-neostigmine administration during kidney transplantation on the functioning of the transplanted kidney. In the study, medical records of 113 patients who underwent kidney transplantation between January 2015 and December 2018 were examined. Out of these records, 47 were excluded because they lacked information about the administration of certain drugs during the transplantation procedure. The drugs of interest were rocuronium, sugammadex, cisatracurium, and neostigmine. Demographic information about the patients and the kidney donors, as well as data on blood urea, creatinine levels, serum and urinary electrolytes, and diuresis were collected. Additionally, information on the type of transplantation (marginal, single, or double), Karpinski scores, and histologic evaluations of the transplanted kidney were gathered. The study observed that the rocuronium + sugammadex group had significantly lower blood creatinine levels at 6, 12, and 24 h than did the cisatracurium + neostigmine group. Similarly, blood urea levels were significantly lower in the rocuronium + sugammadex group for the 24 h following transplantation. However, there were no significant differences between the groups in terms of blood sodium, blood potassium, blood calcium, diuresis, urinary sodium, or urinary potassium levels before and after transplantation. The conclusion was that there was no significant difference in kidney recovery outcomes between the 2 groups [19].

Aminosteroid Neuromuscular Blocking Agents

Aminosteroids are a group of drugs belonging to non-depolarizing neuromuscular blocking agents. Their action is to block the binding of acetylcholine to the motor plate at the neuromuscular junction. This is achieved by competing for a binding site on the alpha subunit of nicotinic receptors. When the concentration of non-depolarizing neuromuscular blocking agents increases at the junction, relative to acetylcholine, it establishes neuromuscular blockade. Aminosteroids include pipecuronium, pancuronium, vecuronium, and rocuronium, among others [20].

Pipecuronium and Its Use in Reduced Kidney Function

Pipecuronium is a long-acting steroidal neuromuscular blocking agent. It has an excellent safety profile. Its structure is similar to that of pancuronium, but the difference is that it has no cardiovascular effect. It is characterized by a long clearance (0.16 L/h/kg) and long elimination half-life (2 h). The elimination is largely through the kidneys. Patients with renal failure have shown a prolonged elimination half-life (275 min vs 127 min in healthy patients) and reduced clearance (1.5 vs 2.5 $mL \times kg^{-1} \times min^{-1}$). Therefore, this drug is not indicated in such patients [21-23].

Pancuronium and Its Use in Reduced Kidney Function

Pancuronium is a long-acting, bis-quaternary aminosteroid and neuromuscular blocking agent. It was first synthesized in 1964. Subsequently, this drug fell out of common use following the advent of neuromuscular blocking drugs with intermediate duration of action, such as rocuronium and vecuronium. In addition, the drug had a long elimination time and a context-sensitive half-life and mainly renal clearance. Samogyi et al found that renal insufficiency can affect the duration of action of pancuronium bromide in 2 ways. These are the distribution and elimination of the drug, which are associated with a fairly short or significantly prolonged duration of action. The clearance is decreased and elimination half-life prolonged in renal failure. In patients with renal failure, pancuronium can cause prolonged paralysis. The clearance is reduced by one-half to two-thirds, while the volume of distribution is minimally affected. Metabolites, especially 3-hydroxypancuronium, whose excretion is impaired by a renal issue, have some neuromuscular blocking activity and further prolong paralysis. This results in a 2-fold to 4-fold prolongation of the elimination phase half-life [24-27].

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Vecuronium and Its Use in Reduced Kidney Function

Vecuronium is a non-depolarizing neuromuscular blocking agent. Vecuronium inhibits depolarization and blocks acetylcholine from motor endplate binding. It is mainly metabolized in the liver, but studies have shown that it has prolonged clearance in patients with renal failure. It has an active metabolite called 3-desacetyl vecuronium, which relies mainly on kidney elimination. There was a study conducted by Segredo et al in which a group of patients that had impaired renal function (clearance of creatinine less than 30 mL/min) had higher plasma concentrations of 3-desacetyl vecuronium. The conclusion was that patients with kidney failure and high levels of 3-desacetyl vecuronium were associated with prolonged neuromuscular blockade. This shows that renal function has a significant role in patients' recovery from vecuronium neuromuscular blockade [4,28].

In conclusion, lower doses of vecuronium should be administered and repetition of these doses should be avoided in patients with kidney failure. Use of a different neuromuscular blocking agent than vecuronium should be considered, namely, a drug which is not metabolized in the kidney. In patients with renal diseases, when vecuronium is the only available option, careful monitoring should be performed, such as train-of-four monitoring [28].

Rocuronium and Its Use in Reduced Kidney Function

Rocuronium is a non-depolarizing muscular blocking agent. It is a pancuronium analogue, which has faster action onset and shorter duration than atracurium and vecuronium. A single bolus of intravenous rocuronium has a very fast onset time and low potency [29]. Rocuronium bromide binds to post-junctional nicotinic acetylcholine receptors, which blocks the effect of acetylcholine and therefore inhibits contraction of muscles [1].

Rocuronium is excreted in urine (10-25%), in unchanged state, and in bile (more than 70%). Both kidney and liver insufficiencies decrease clearance and increase time of their action. A decrease in hepatic blood flow, for example in pneumoperitoneum for laparoscopic gynecological surgery, affects both the duration and action of rocuronium [4,30,31].

In end-stage renal disease, the clearance of rocuronium is decreased and duration of its action can be significantly prolonged. It is suggested that in patients with end-stage renal disease, extrarenal clearance of rocuronium can happen. Plasma concentrations of rocuronium after 12 h of sugammadex injection are much higher in patients with end-stage renal disease [30,31].

Effect of Ulinastatin on Skeletal Muscle Relaxants in Patients with Reduced Renal Function

Studies have provided evidence that the administration of ulinastatin, along with remifentanil or intravenous fluids, prior to neuromuscular blockade with the non-depolarizing muscle relaxants rocuronium, vecuronium, cisatracurium, atracurium, mivacurium, and pancuronium can lead to a prolonged onset time in patients with various conditions. These conditions include infection, oculopharyngeal muscular dystrophy, congenital heart defects, kidney failure, and liver cirrhosis. The use of ulinastatin in combination with these medications and fluids has been shown to delay the onset of non-depolarizing muscle relaxants, potentially affecting the effectiveness and duration of muscle relaxation. Therefore, healthcare professionals should consider this interaction and adjust the dosage and timing of medications accordingly in patients with these conditions [32]

Neostigmine and Sugammadex Characteristics

Neostigmine and sugammadex are medications used in clinical practice to reverse neuromuscular blockade, but they have different mechanisms of action and effects on kidney function [33].

Neostigmine is a commonly used agent for reversal of neuromuscular blockade. It is a small molecule that belongs to a class of drugs called cholinesterase inhibitors. It is indicated in the treatment of some neuromuscular diseases like myasthenia gravis, but also works as an antagonist of the effects of neuromuscular blocking agents, which are drugs used to induce muscle relaxation during surgery. Neostigmine works by inhibiting the activity of acetylcholinesterase, an enzyme that is responsible for the degradation of the neurotransmitter acetylcholine. By interfering with acetylcholinesterase, neostigmine inhibits the breakdown and increases the levels of acetylcholine, leading to increased muscle tone and contractility [34].

Sugammadex, introduced in 2008 in Europe, is an innovative compound designed to counteract the effects of steroidal neuromuscular blockers. It acts as a selective agent, binding primarily to muscle relaxants such as rocuronium and, to a lesser extent, vecuronium. Its primary purpose is to reverse the neuromuscular blockade induced by this category of muscle relaxants known as steroidal non-depolarizing neuromuscular blockers. Sugammadex operates by enveloping and deactivating rocuronium on a molecular level, rendering it water-soluble and facilitating its swift elimination from the body. Importantly, unlike traditional anticholinesterase reversal agents like neostigmine, sugammadex does not extend the duration of acetylcholine's action at the neuromuscular junction [35].

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Use of Reversal Agents in Reduced Renal Function

In 2016, Isik et al conducted a study to assess the impact of sugammadex and neostigmine on renal biomarkers in patients undergoing elective surgery. The research aimed to compare the effects of these drugs on kidney function, utilizing specific biomarkers such as the novel marker cystatin C. Unlike creatinine, cystatin C is a sensitive indicator of renal function since it remains unaffected by factors such as age, sex, muscle mass, and diet, even as the GFR drops below 50 mL/min/1.73 m^2. The study involved 50 patients aged 18 to 65 years scheduled for elective surgery under general anesthesia. These patients exhibited normal kidney function (serum creatinine <1.5 mg/dL) and fell within the American Society of Anesthesiologists (ASA) classification as ASA class I-II. They were divided into 2 groups: one was administered sugammadex and the other neostigmine. Serum levels of cystatin C, creatinine, urea, blood urea nitrogen, sodium, potassium, and calcium, as well as urine levels of α1-microglobulin, β2-microglobulin, and microalbumin, were measured before and after drug administration. Patients were randomly assigned to the neostigmine group (n=25) or the sugammadex group (n=25). At the conclusion of the surgery, the sugammadex group received 4 mg/kg of intravenous sugammadex, effective for reversing moderate and deep neuromuscular blockade. In contrast, the neostigmine group received a combination of 0.04 mg/kg neostigmine with 0.01 mg/kg atropine intravenously upon the reappearance of a second twitch of train-of-four after the final rocuronium dose. This was necessary since neostigmine lacks the efficiency to reverse deep neuromuscular blockade. The study assessed and compared the renal markers influenced by sugammadex and neostigmine.

The results indicated a significant rise in postoperative β2-microglobulin levels in the sugammadex group, compared with preoperative values. This suggested the influence of sugammadex on β2-microglobulin levels, an essential indicator of renal tubular dysfunction. Similarly, postoperative α1-microglobulin levels increased significantly in the sugammadex group, reflecting potential renal tubular dysfunction. In the same group, postoperative microalbumin levels significantly increased, indicating potential harm to the glomerular barrier [36]. Interestingly, cystatin C levels in the sugammadex group showed no significant change between preoperative and postoperative values, suggesting minimal impact on glomerular function – a distinct marker for this aspect of kidney performance.

Overall, the study demonstrated that sugammadex influenced renal function, as evident from changes in β2-microglobulin, α1-microglobulin, and microalbumin levels. Nonetheless, its effects were better tolerated by the kidneys than those of neostigmine. While demographic data showed no notable differences between the 2 groups, distinctions emerged in postoperative biomarker levels. In the neostigmine group, levels of α1-microglobulin and cystatin C increased significantly, indicating a negative effect on kidney function. The primary significant difference between the 2 groups was observed in cystatin C levels, with the neostigmine group showing higher values than the sugammadex group. This discrepancy indicates that neostigmine has more detrimental effects on glomerular filtration activity.

Based on these findings, the researchers concluded that sugammadex has a more favorable effect on kidney function, when compared with neostigmine. However, both drugs affected kidney function when contrasted with preoperative values. While they did not lead to renal failure, they had the potential to worsen preexisting conditions.

Notably, the liver metabolism of neostigmine can indirectly influence renal function. Thus, monitoring renal function during neostigmine administration remains crucial, particularly in patients with existing renal impairments. The study underscored the significance of employing specific and sensitive biomarkers like cystatin C to accurately evaluate kidney function. Further research is imperative to better comprehend the long-term renal effects of these drugs and assess their safety in patients with compromised kidney function [36].

Use of Sugammadex as Reversal for Rocuronium and Its Effect on Renal Function

Uludağ et al conducted a study in 2021 that delved into the potential nephrotoxic effects of sugammadex and the combination of rocuronium with sugammadex in rats. The primary objective was to assess kidney tissue histopathology and antioxidant after drug administration. Their experiment involved 32 rats, organized into 4 groups: sham (group 1), control (group 2), sugammadex (group 3), and rocuronium plus sugammadex (group 4). Kidney tissue was scrutinized for histopathological changes and antioxidant levels.

Remarkably, group 4, which received rocuronium along with sugammadex, exhibited a marked reduction in glutathione levels, compared with the other groups. This combined group also displayed notably elevated malondialdehyde levels, a telltale sign of free radical-induced damage, when compared with all other groups. Histopathological evaluation of the kidney tissue in group 4 indicated increased vascular congestion, degeneration in dilated tubules and tubule epithelium, and dilatation in glomerular capillaries and veins in the medulla region.

Consequently, the authors concluded that administering rocuronium in conjunction with sugammadex within the studied dose ranges caused detrimental histopathological changes

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in rat kidneys. The authors cautioned about potential nephrotoxic effects in humans, even though they acknowledged the study's limitation in being conducted solely on rats. The authors stressed the necessity for further research to ascertain if humans are similarly affected [36].

Comparison of Effects of Chosen Reversals on Graft Function During Renal Transplantation

Vargas et al conducted a retrospective, case-control study in 2021. Their objective was to compare the effects of sugammadex plus rocuronium with those of neostigmine plus cisatracurium on graft function during renal transplantation. Notably, rocuronium can be used in patients with severe renal failure, but its duration of muscle relaxation increases, leading to a higher risk of postoperative residual neuromuscular block. This is due to the variable elimination of the rocuronium-sugammadex complex, influenced by renal function. This study aimed to shed light on the effects of this complex on transplanted kidney function, as the newer compound. Sugammadex is less understood than neostigmine.

The research encompassed 113 medical records of kidney transplant patients spanning from January 2015 to December 2018. After exclusions, data from 66 medical records were analyzed, revealing that creatinine levels at various time points were significantly lower in the rocuronium plus sugammadex group than in the cisatracurium plus neostigmine group. Similarly, blood urea levels for 24 h after transplantation were significantly lower in the rocuronium plus sugammadex group. Importantly, no significant differences were observed in blood sodium, blood potassium, blood calcium, diuresis, urinary sodium, or urinary potassium levels before and after transplantation between the 2 groups.

This retrospective investigation indicated that the rocuronium-sugammadex strategy might yield improved postoperative kidney function during renal transplantation. However, the authors acknowledged limitations in study design and sample size, highlighting the necessity for further research to comprehensively understand the effects of sugammadex on kidney function in the context of transplantation. Nevertheless, the available evidence points to sugammadex as the preferred and safer choice for reversing rocuronium-induced neuromuscular blockade in patients undergoing kidney transplantation.

Summing up the collective studies, sugammadex generally demonstrates a safer impact on kidney function, when compared with neostigmine. The investigations encompassed various contexts, including in vitro, in vivo, and clinical trials involving patients with both normal and compromised kidney function, as well as those undergoing kidney transplantation. While both drugs exert minimal effects on renal glomerular filtration and tubular functions, the disparity leans toward sugammadex, which exhibits a slightly milder impact than neostigmine.

Importantly, cystatin C, a specific marker of glomerular function, was significantly higher in the neostigmine group in one study, indicating sugammadex's potential advantage in preserving renal function. However, each patient's response can differ based on parameters such as drug dosage and existing renal conditions. Given that both drugs provoke fluctuations in various kidney function markers, additional research is crucial to establishing their safety profiles. Caution is advised, and these drugs should be administered carefully, accounting for a patient's preoperative renal status [19].

Summary of the Use of Muscle Relaxants and Relaxants in Impaired Renal Function

As previously mentioned, impaired kidney function can affect the action of skeletal muscle relaxants. Recommendations regarding the use of drugs to reverse neuromuscular blockade and its monitoring were included in the 2020 Guidelines on Muscle Relaxants and Reversal in Anaesthesia prepared by the French Society of Anaesthesia and Intensive Care. They also contain recommendations for patients with impaired kidney function. According to these recommendations:

- it is probably recommended to use of a benzylisoquinoline muscle relaxant (atracurium/cisatracurium) in cases of renal/hepatic failure,
- it is probably recommended, administer it at the usual dose when using sugammadex in cases of renal failure
- it is recommended not to modify the initial dose in renal/hepatic failure patients, irrespective of the type of muscle relaxant used [37].

Table 2 summarizes the associations between skeletal muscle relaxants and impaired kidney function [3,13,15-19,21-32,38].

Future Directions

Some of the research was conducted on animal models. Therefore, further research and reports are needed to assess the long-term effects of these agents on kidney health, especially in high-risk patient populations. Technological advancements enable more precise intraoperative monitoring of skeletal muscle relaxant effects. It should be remembered that the train-of-four should always be used when performing neuromuscular blockade.

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Table 2. Impact of the clinical use of skeletal muscle relaxants depending on their route of elimination in reduced renal function.

Drug	Path of elimination and metabolism	Clinical impact in impaired kidney function
Rocuronium	Excretion by bile (70%), and in urine (10-5%)	Decreased clearence and prolonged time of action
Vecuronium	Excretion mainly by liver, active metabolite called 3-desacetyl vecuronium relies mainly on kidney elimination	• Prolonged neuromuscular blockade in patients with kidney failure can happen • Lower doses of vecuronium should be administered and repetition of these doses should be avoided in patients with kidney failure • Use of a different neuromuscular blocking agent than vecuronium should be considered
Pancuronium	Excretion by kidneys in 80%; hepatic degradation in 10% and biliary excretion in 10%; active metabolite excreted in major by kidneys	• Decreased clearance • Prolongation in elimination phase half-life in renal failure • Can cause prolonged paralysis
Pipecuronium	Excretion mainly by kidneys. About 40% of pipecuronium is excreted unchanged by kidneys together with another 15% as 3-hydroxypipecuronium in 24 h	• Prolonged half-life and reduced clearance • Use is not indicated in such patients
Cisatracurium	Metabolized in liver through Hofmann elimination; metabolites are excreted primarily through the urine	• In patients with renal impairment clearance can be reduced and lead to prolonged effects of drug
Mivacurium	Metabolized in liver through ester hydrolysis by plasma cholinesterase	• Neuromuscular block is not significantly influenced by renal function • In patients with preterminal renal failure, prolonged recovery from the neuromuscular blockade can happen • Prolonged neuromuscular block in patients with end-stage renal disease
Atracurium	Metabolized primarily in the liver, with minimal involvement of the kidneys in excretion	• No need in dose adjustments or alterations in the administration in patients with impaired kidney function
Succinylcholine	Plasma pseudocholinesterase	• If no associated neuropathy or preoperative hyperkaliemia, considered safe in patients with renal failure • In patients with renal failure repeated doses of succinylcholine should be avoided

Conclusions

Kidney function is a significant factor in the effects of aminosteroid non-depolarizing neuromuscular blocking agents. The duration of action of pancuronium, vecuronium, and rocuronium are prolonged in kidney disease. The benzylisoquinoline non-depolarizing drugs atracurium and cisatracurium can be safety used in patients with kidney disease because they are metabolized in the plasma by Hoffmann degradation and ester hydrolysis. However, the duration of action of mivacurium is prolonged in patients with kidney disease because the plasma cholinesterase activity is decreased. The same applies to succinylcholine, the only depolarizing neuromuscular blocking agent currently used.

Institution Where Work Was Performed

The article was written in Collegium Medicum University of Warmia and Mazury, Olsztyn, Poland.

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