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NEUROMUSCULAR BLOCKADE (GS MURPHY, SECTION EDITOR)

Mivacurium: a Review

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Abstract

Purpose of Review Mivacurium is a short-acting non-depolarizing neuromuscular-blocking agent (NMBA) which has recently been re-released onto the US market. This review provides a brief overview about the pharmacology of mivacurium and discusses its use in recent clinical practice.

Recent Findings Mivacurium has been reported to be especially useful in the pediatric population, especially for shorter cases, and infusions can be used for longer cases without inducing tachyphylaxis. As it is rapidly metabolized by pseudocholinesterase (PChE), mivacurium does usually not require a specific reversal agent to offset its actions at the end of surgery. Especially for use in short cases, this makes it a potentially advantageous alternative to the use of other NMBA. However, deficiencies in PChE as well as old age and some drug interactions can be associated with prolonged neuromuscular blockade. The rapid administration of higher doses may provoke significant histamine release leading to hemodynamic compromise.

Summary Despite other NMBA being available on the market and its side effects, mivacurium may still be a useful agent in short cases, particularly in the pediatric population.

Keywords Mivacurium · Neuromuscular-blocking agent · Pseudocholinesterase deficiency · Cardiovascular instability · Drug interactions

Introduction

Mivacurium chloride is a short-acting, non-depolarizing neuromuscular-blocking agent (NMBA) which was first synthesized in 1981. It belongs to the benzylisoquinolinium group. Although muscle relaxation with mivacurium can principally be extended to any duration of surgery, it may be best suited to short surgical procedures, where rapid recovery without the need for reversal may be advantageous. Interestingly, and possibly related to either the non-availability or the high costs of the reversal agent sugammadex, mivacurium has recently been re-released in the USA after previous discontinuation of sales in 2007.

The aim of this article is to briefly review the pharmacology of mivacurium, with particular emphasis on its side effects and its current use in clinical practice. We also discuss the need for such NMBAs in an era where alternative agent-reversal strategies (i.e., rocuronium-sugammadex) are readily available.

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Review

Clinical Pharmacology

Mivacurium is a short-acting, highly selective benzylisoquinolinium consisting of three isomers in an acidic solution with a pH of 4.5. As with all NMBA, mivacurium is a competitive antagonist of acetylcholine at the postsynaptic nicotinic receptors. An additional phenolic group sets its structure apart from atracurium. Mivacurium does not undergo Hoffman degradation—it relies predominantly on plasma pseudocholinesterase (PChE) for metabolism, and, although only infrequently found, any deficiency will result in a prolongation of the neuromuscular block.

Mivacurium exists in three different structural states: the trans-trans, cis-trans, and cis-cis stereoisomers. The initial two stereoisomers are the most commonly occurring, comprising 92–96% of commercially available mivacurium. They have also been found to be the most potent of the three stereoisomers. The metabolites of all stereoisomers have no clinically significant cardiovascular, neuromuscular, or autonomic activity. The metabolism of the trans-trans and cis-trans isomers occurs by enzymatic hydrolysis via PChE to form a quaternary alcohol and a quaternary mono-ester metabolite. The cis-cis isomer is the least potent isomer, with a slower, PChE-independent clearance.

Limited tissue distribution, along with a high clearance rate, results in a short half-life. The clearance rates, elimination half-life, and mean volume of distribution of the isomers are listed in Table 1.

The metabolites of mivacurium are excreted via urine and bile, along with a small portion of the unchanged drug. The half-life of mivacurium is approximately 2 min, which is shorter than the onset time of a typical intubating dose (two times its ED_{95}, see below) of the drug (2–3 min) [1].

Time to spontaneous recovery varies according to the initial intubating dose. Lower doses are associated with a faster 95% spontaneous recovery time which is 21–34 min in adults after doses of 0.1–0.25 mg/kg, respectively. Doses of 0.2 mg/kg in children have a 95% spontaneous recovery time of 19 min.

Clinical Use

Endotracheal Intubation

The ED_{95} (dose required to suppress 95% of the response of the adductor pollicis brevis muscle to a supramaximal single-twitch ulnar nerve stimulation) of mivacurium is 0.07 mg/kg (0.06–0.09 mg/kg) when using opioid/nitrous oxide or opioid/oxygen anesthesia. The clinical onset time of the standard intubating dose (2× ED_{95}) of 0.14 mg/kg is approximately 2–3 min. As with all NMBA, lower doses of mivacurium result in a delayed onset time, whereas higher doses facilitate a quicker onset. However, with the use of higher doses, there is a risk of hypotension, especially in adults, secondary to histamine release, and such side effects will limit the maximum safe dose (see "Side Effects" section). Perioperative repeat dosing of mivacurium with 0.1 mg/kg results in an additional 15 min of neuromuscular blockade [1, 2].

In children aged 2–12 years, the ED_{95} is reportedly higher, 0.1 mg/kg. Consequently, a dose closer to 0.2 mg/kg may be used for intubation. Children also recover faster than adults from the effects of mivacurium, and less histamine release-related side effects have been reported [3•]. However, in very young children (2 months to 2 years), the ED_{95} is 0.07 mg/kg [1, 2]. The use of an intubating dose closer to a 3x ED_{95} may have the advantage of a significantly faster (30 s) onset time in children aged 2–12 months, accelerating onset time by approximately 30 s. Interestingly, this effect was not observed in children aged 13–35 months, 3–6 years, and 7–14 years [3•]. As per the manufacturers information, mivacurium has not been tested in infants less than 2 months of age, so the safety in this group has not been established. Modolo et al. [4] compared the onset time and duration of action of rocuronium, atracurium, and mivacurium in children aged 30 months to 12 years, and reported that mivacurium had a significantly longer onset time, but also a significantly shorter time to neuromuscular recovery. A transient, clinically insignificant, decrease in blood pressure was observed in the mivacurium group [4].

Significant train of four (TOF) fade is not always seen with mivacurium, and according to the manufacturers information sheet, it may be possible to intubate before complete abolition of the adductor pollicis TOF ratio has occurred [1, 2]. However, this may not be easily implementable in clinical practice in the absence of reliable quantitative neuromuscular monitoring. No tachyphylaxis has been noted with infusions of mivacurium, neither have there been any reports of cumulative neuromuscular effects with repeated doses of mivacurium [1].

Table 1 Clearance rates, elimination half-life, and volume of distribution [1, 2]

Stereoisomer	Clearance (mL/kg/min)	Elimination half-life (min)	Vol of distribution (mL/kg)
Trans-trans	53	2	147 (67–254)
Cis-trans	99	1.8	276 (79–772
Cis-cis	4.6	53	335 (192–553)

Unwanted Effects

Prolonged Duration of Action

The clearance of mivacurium in the elderly may be prolonged, resulting in an increase in the duration of action by 20–30% [1]. In patients with renal and hepatic impairment, the dose should also be reduced, as decreased levels of PChE have been reported. Prolonged duration of mivacurium-induced neuromuscular block has been noted in patients with renal impairment by a factor of up to 1.5, and a factor of 3 in patients with hepatic impairment due to decreased clearance levels in the latter patients [1, 2, 5•].

Although animal models suggest no specific risk, the use of mivacurium in pregnancy should only be recommended if the expected clinical benefit outweighs the risks to the fetus. Mivacurium has been used successfully in several case reports

during cesarean section procedures. However, consideration must be given to the decrease in PChE levels observed from the second trimester of pregnancy. Though it is unknown whether mivacurium is excreted into the breast milk, it appears unlikely that any NMBA potentially transferred to a newborn would have significant effects [1, 2].

As discussed, mivacurium relies on PChE for rapid ester hydrolysis. PChE is structurally similar to acetylcholinesterase and is hepatically synthesized. Patients with PChE deficiency are usually asymptomatic; however, exposure to mivacurium or suxamethonium may lead to prolonged blockade [5•, 6]. Genetic inheritance of the PChE deficiency is autosomal recessive in most cases. The underlying genetic mutation is located on the arm of chromosome 3 and associated with the butyrylcholinesterase gene. According to Soliday et al. [5•], 65 genetic variants can result in the deficiency for PChE, resulting in minimal or extreme prolongation in neuromuscular blockade. The dibucaine or fluoride number, if known, may provide some guidance. The exact incidence of PChE deficiency is unclear (possibly 1:3000–5000), and many patients live an unaffected life until they are exposed to mivacurium or suxamethonium. The total absence of functional PChE is extremely rare (1:100,000). However, the Vysya community in India has a reported incidence of 4% [5•].

A number of case reports have described PChE deficiency and its association with a prolongation of neuromuscular block. Most of these patients had known clinical risk factors—renal or liver disease, malnutrition, pregnancy, or were taking medications that interacted with PChE levels (see "Drug Interactions" below) [7–9]. However, some patients had no risk factors and were found to have homozygous variants of genetically inherited PChE deficiency [10].

Another groups of patients at risk of lower PChE activity are patients with significant burns. Decreased levels of PChE have been reported in burns patients at days 5–6, with the level of PChE reduction correlated to the severity of the injury. In addition to the aforementioned effect, burn injuries may also prolong the onset time of mivacurium [11]. This is thought to be due to the well-described effect of an increased resistance of the neuromuscular endplate due to an increase in receptor numbers and conversion into more sensitive juvenile acetylcholine receptors. The results in adults were found to be statistically significant. The delayed recovery from the effects of mivacurium appears to be directly related to a reduction in PChE activity. These effects may be more pronounced in adults and less significant in children [12, 13].

Drug Interactions

Mivacurium is potentiated by volatile anesthetic agents such as isoflurane and enflurane, which consequently decrease mivacurium infusion requirements by 35–40% [1, 2]. Tercan et al. [14] found that the action of mivacurium was prolonged with the use of metoclopramide or ondansetron. An intubating dose of 0.2 mg/kg was used and two groups were given either metoclopramide 15 mg or 4 mg ondansetron. The third group received normal saline. The metoclopramide group had significantly longer T_{25}, T_{50}, T_{75}, and T_{90} recovery indices when compared with the normal saline group. The ondansetron group had a longer T_{25} and T_{75} recovery when compared with the normal saline group. Both anti-emetic groups showed decreased PChE levels post administration of the study drug, and all three groups had a further decrease in levels 5-min post administration of mivacurium [14]. A further study by Skinner et al. also noted a decreased PChE level after administration of metoclopramide [15]. Correspondingly, Motamed et al. observed a faster onset time for mivacurium when co-administered with metoclopramide and also reported a prolonged block. Metoclopramide decreases PChE levels, thereby affecting the metabolism of mivacurium [16].

Antidepressants such as fluoxetine, sertraline, and amitriptyline are inhibitors of cholinesterases, with sertraline being the most potent inhibitor of the three [17]. PChE levels may also be decreased by oral contraceptives and bambuterol, with the latter causing a 90% inhibition of PChE [5•].

Side Effects

Mivacurium, like many other benzylisoquinolinium NMBAs, is known to trigger a release of histamine, which may have an impact on cardiovascular stability on induction. Higher doses have been associated with better intubating conditions; however, more rapid injection of higher doses appears to be associated with more significant effects. Plaud et al. [18•] in a randomized study investigated the effect of various mivacurium doses on the mean arterial blood pressure (MAP). After induction of anesthesia with etomidate, fentanyl, and mivacurium, they assessed the change in MAP in both normotensive and hypertensive patients. They detected a significant decrease in MAP in hypertensive, but not normotensive patients, after rapid (10 s) administration of mivacurium. The effect was less pronounced when mivacurium was given more slowly (30 s). A decrease in MAP may also be seen in obese patients if the actual, rather than ideal, body weight is used for calculation of the mivacurium dose [1, 18•]. In adults, it is hence recommended that higher doses are given over a longer period of time (i.e., 30–60 s) to minimize the cardiovascular side effects. However, this dosing may affect the onset time of the drug.

Overall, it appears that the problem of mivacurium-provoked histamine release may be lower in children. However, several cases of bronchospasm have been reported following the use of mivacurium. Erol et al. [19] report a case

of bronchospasm in a child with adenoid hypertrophy. Children with adenoid hypertrophy may be predisposed to allergic reactions, and so, special caution must be taken when using histamine-inducing drugs in this population or in patients with asthma [20]. This side effect is not confined to children with underlying medical conditions, as Fine et al. describe mivacurium-induced mild subclinical bronchoconstriction in ASA I and II patients [21]. Two further cases of bronchospasm were reported by Bishop et al [22]. It is important to note that the Food and Drug Agency reports a significantly higher proportion of adverse effects with mivacurium compared with other non-depolarizing muscle relaxants. Although children do not appear to demonstrate the same extent of mivacurium-provoked histamine release as adults, it must be remembered that any reactions may be more severe due to their immature cardiovascular and respiratory systems [23].

Specific Clinical Applications

Overall, mivacurium may be a suitable NMBA, especially when cases are short and reversal is either undesirable or unavailable. It is beyond the scope of this short review to provide more specific information in this regard. In the following, two specific uses for the drug are separately described.

Successful use of mivacurium has been reported in patients with neuromuscular diseases. Traditionally, in this group of patients, NMBAs are frequently avoided due to the unpredictable duration of action. Nagele and Hammerele [24] successfully used mivacurium and sevoflurane in a patient with Huntington's chorea. There were no intraoperative complications and the patient was extubated successfully without any prolonged effects. Munster and Schmidt [25] used mivacurium in patients with multicore disease. Ulke and Senturk reported excellent intubating conditions when using a relatively low (0.1 mg/kg) dose of mivacurium in 112 patients with myasthenia gravis. Only two required prolonged intubation and postoperative ICU admission [26].

A relatively novel use of mivacurium is its addition to lidocaine for the implementation of a Biers block. Mizrak et al. [27] assessed its use in day surgery patients booked for a carpal tunnel release and noted a quicker onset time for sensory and motor block. However, patients developed a prolonged motor block. The use of mivacurium did result in a decrease in postoperative analgesia requirements, and facilitated surgery by enhancing muscle relaxation.

Discussion: Mivacurium Use in 2018?

Leaving specific contraindications aside, mivacurium appears to be a suitable NMBA for use in every anesthesia practice. Its relatively short duration of action and (relatively) organ-independent metabolism may be beneficial especially in shorter cases. As the recovery index (T_{25}-T_{75}) of mivacurium is extremely steep, reversal with cholinesterase-inhibitors may not be required to offset its clinical effects. The latter may be of specific interest in cases where neostigmine or sugammadex reversal may not be desirable.

However, though mivacurium may be classified as a short-acting NMBA, one of the most significant problems limiting its clinical use is the variation in its duration of action. This problem is not unique to mivacurium, but can be observed across all NMBAs. However, all other NMBAs currently on the market are best classified as intermediate- or long-acting agents. The unique feature of mivacurium is its shorter duration of action and possibility that reversal agents may not be required to achieve full neuromuscular recovery. The expectation of a fast recovery may provide a false sense of security and result in postoperative residual neuromuscular blockade with all its detrimental effects. In this context, it should be emphasized that only neuromuscular monitoring can provide sufficient security to avoid residual blockade.

A further problem of mivacurium may be its relatively strong potential to trigger a significant histamine release. Cardiovascular instability, as well as bronchospasm, has been described following its administration. As mivacurium has a slow onset of action, it is likely very counter-intuitive to the clinician to inject an intubating dose over the period of 30 s–1 min. However, the latter may be one of the most efficient ways to avoid significant side effects. Consequently, intubating conditions after a standard 2x ED_{95} are likely to be inferior (depending on timing) to that resulting from the use of other currently used NMBAs. This may exclude mivacurium from scenarios with the need for a rapid muscle relaxation. Since the re-introduction of mivacurium to the US market in 2016, sugammadex has been approved in the USA to reverse the effects of amino-steroidal NMBA (2015). Hence, a combination of a fast-acting intermediate duration NMBA with a fast and reliable reversal is available. To reverse the effects of both, amino-steroids and benzylisoquinolinium NMBA, a novel agent, calabadion, may eventually become available [28].

If costs are an issue, the combination of rocuronium-sugammadex (50 mg/200 mg) currently costs approx. USD 102.50. Comparing the expenses for mivacurium (20 mg @ approx. USD 30) [29], the short duration of action of mivacurium (and hence the need to re-dose in any but the shortest cases) could possibly offset the costs of a more liable combination. Hence, from an economic point of view, mivacurium may best be confined to very short cases which do not require more than a few minutes of deeper neuromuscular block.

Conclusion

Mivacurium is of specific interest for short cases (no need for re-dosing) in pediatric anesthesia (less risk of histamine release). If sugammadex is unavailable, it may also be a useful drug to provide neuromuscular block as its rapid recovery profile is likely to not require reversal. However, its duration of action, though generally short, is affected by several clinically significant comorbidities and is certainly not sufficiently reliable to avoid residual block. It is emphasized that only neuromuscular monitoring can achieve this goal.

Compliance with Ethical Standards

Conflict of Interest Lisa S. Molloy declares that she has no conflict of interest. Thomas Ledowski has received speaker's honoraria and is supported by a non-related research grant from MSD, the manufacturer or rocuronium and sugammadex.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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