Clinical use of sugammadex

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Until recently the only antagonists of residual neuromuscular block available for clinical use have been acetylcholinesterase inhibitors, such as neostigmine. Cyclodextrins comprise a family of cyclic oligosaccharides that have previously been used in anaesthesia to formulate a variety of different drugs used in anaesthesia including propofol, etomidate, bupivacaine, sufentanil and intranasal midazolam. Sugammadex is a modified γ cyclodextrin specifically designed to encapsulate rocuronium and other amino steroidal muscle relaxants that are chemically similar such as vecuronium [1,2].

Mode of action of sugammadex

The underlying mechanism of action is new and differs completely from that of acetylcholinesterase inhibitors. When sugammadex is introduced into the blood, the free molecules of rocuronium in plasma which are in equilibrium with the tissues are almost immediately captured by the sugammadex molecules and the plasma free rocuronium concentration decreases very rapidly. This creates a gradient of rocuronium between tissue and plasma, which results in rocuronium molecules moving out of the tissue and into plasma where they are also encapsulated by free sugammadex molecules. Whether diffusion of sugammadex onto the tissues and formation of complexes at the neuromuscular junction occurs remains uncertain. Following administration of sugammadex, the concentration of free rocuronium decreases rapidly in the plasma but the total rocuronium plasma concentration (free and bound to sugammadex) increases rapidly [3]. Thereafter the rocuronium-sugammadex complex is rapidly filtered by the glomerulus and eliminated through the kidney. Sugammadex has no direct effect on cholinergic transmission and consequently is described as a selective relaxant binding drug (SRBA). Sugammadex does not exhibit intrinsic biological activity.

Sugammadex selectively reverses steroidal neuromuscular blocking agents (NMBA), particularly rocuronium but also vecuronium. Its selectivity for steroidal NMBA over atracurium or succinylcholine is due to the size of its inner cavity and its molecular structure which confers complementarity with the right hydrophobic steroidal skeleton. Sugammadex has no affinity for more than 40 drugs that may be used during anaesthesia (hypnotics, analgesics, antibiotics, cardiovascular drugs). Affinity for cortisone, hydrocortisone and aldosterone has been extensively studied because of the strong binding between sugammadex and steroidal NMBA, where the affinity for these drugs is 120 fold less than that for rocuronium. Affinity for atropine, verapamil, ketamine is 400 to 700 fold lower than for rocuronium. Among many molecules studied, toremifene, fucidic acid and flucloxacillin are the only molecules known to displace rocuronium or vecuronium from sugammadex. Based on theoretical simulations, sugammadex could capture hormonal contraceptives and induce a decrease in unbound progestagen. This effect is equivalent to taking the contraceptive pill 12 hours too late [4].

Clinical studies

Moderate levels of rocuronium-induced neuromuscular block are consistently and effectively reversed by sugammadex. A phase II study in adult patients has shown that sugammadex administered at reappearance of T2 of the train–of-four (TOF) reversed 0.6 mg/kg rocuronium-induced neuromuscular block in a dose-dependant manner. At doses of sugammadex at or above 2.0 mg/kg recovery occurred within 3 min without any sign of recurarisation [5]. When compared with neostigmine for reversal of neuromuscular block at reappearance of 4 TOF responses it has been shown that a TOF ratio of 0.9 was obtained in approximately 2 minutes with sugammadex compared to a time of 17 minutes using neostigmine. Moreover, 2–4 mg/kg sugammadex when given at the reappearance of T2 in prolonged rocuronium-induced block (>2hours) effectively reversed rocuronium. Recently Blobner et al compared two groups of patients, randomly allocated to receive either sugammadex 2.0 mg/kg or neostigmine 50 µg/kg with glycopyrrolate 10 µg/kg at reappearance of the second response of the TOF (mean 16% of twitch height of first response) after the last dose of rocuronium. Time to recovery of the
TOF ratio to 0.9 after sugammadex compared with neostigmine was significantly shorter (P < 0.0001), being 1.5 minutes compared with 18.6 minutes. Predictability of response was also greater with sugammadex than neostigmine, with 98% of sugammadex patients versus 11% of neostigmine patients recovering to a TOF ratio of 0.9 within 5 min. However it took 101 min to establish a 98% predictability of a recovery of the TOF ratio to 0.9 in the neostigmine group [6].

Although sugammadex was developed to antagonise rocuronium-induced block, it is also effective in reversing 0.1 mg/kg vecuronium-induced block. When given at reappearance of T2, recovery to a TOF ratio of 0.9 was obtained in 2.3 minutes and 1.5 minutes following 2.0 and 4.0 mg/kg respectively. Even if recovery is slightly slower than when reversing a rocuronium-induced block, it is 6 times shorter than when using neostigmine [7].

Several studies have demonstrated that there are no differences in time taken to reach a TOF ratio of 0.9 after anaesthesia maintained with halogenated agents when compared with propofol [8].

In the presence of a deep level of neuromuscular block (less than 2 responses following the TOF), neither rocuronium nor vecuronium can be reversed satisfactorily in a short period of time using neostigmine. Contrary to neostigmine, increasing the dose of sugammadex allows it to antagonize even deep levels of rocuronium-induced neuromuscular block with the same efficacy and predictability. Profound neuromuscular block (Post-tetanic count: 1 or 2) can be rapidly and safely reversed with sugammadex in humans. With 4 or 8 mg/kg, a TOF ratio of 0.9 could be obtained in 3.3 minutes (range 2.2–4.7 minutes) and 1.5 minutes (1.0–2.1 minutes) respectively [9]. There is clear justification to support the requirement of a higher dose of sugammadex for reversal of a deep block. Sugammadex binds rocuronium on an equivalent molecular basis (i.e. molecule for molecule). The concentration of rocuronium, when reversing a deep block, is likely to be much higher when reversing a superficial block thereby necessitating a larger dosage of sugammadex [4]. Jones et al. have studied the reversal of profound rocuronium-induced block following administration of either 4.0 mg/kg sugammadex or 70 µg/kg neostigmine at reappearance of 1 or 2 responses at the post-tetanic count (PTC)). The average time from injection to recovery of a 0.9 TOF of 0.9 with sugammadex was 2.9 minutes compared with 50 minutes with neostigmine. Most sugammadex patients (97%) recovered to a TOF ratio of 0.9 within 5 minutes after administration whereas 73% recovered between 30 and 60 minutes after neostigmine administration with 23% requiring more than 60 min to recover to a TOF ratio of 0.9 [10].

Succinylcholine has the shortest onset of action of any currently available NMBA. However it has been demonstrated that 1.2 mg/kg rocuronium can provide equivalent intubating conditions in 60 seconds. The use of such a dose results in a long duration neuromuscular block. Nevertheless, there are situations in which deep block must be reversed very rapidly, for example when tracheal intubation has failed. Lee has compared recovery of succinylcholine-induced neuromuscular block with 16 mg/kg sugammadex administered 3 minutes after 1.2 mg/kg rocuronium. Mean time to T1 recovery to 90% of the control value was 6.2 minutes after rocuronium injection and 10.9 minutes after succinylcholine. To summarize, when given, 3 minutes after rocuronium administration, 16 mg/kg sugammadex will completely reverse the block in less than 3 minutes [11].

Although not common, some patients may require anesthesia and tracheal intubation within a few hours of reversal of block. If sugammadex has been used, it is recommended to wait 24 hours before using rocuronium or vecuronium. However, the efficacy of non-steroidal NMBA remain unaffected by the use of sugammadex; Therefore succinylcholine or benzylisoquinolines agents (atracurium, cisatracurium) can be used safely because their neuromuscular blocking properties are unaffected by sugammadex.

**Side effects**

Because sugammadex acts by encapsulation in the plasma and not in the same way as neostigmine (with its action on receptors), it is not expected to have the side effects associated with neostigmine. Sugammadex does not need the concomitant administration either neostigmine or glycopyrrolate. In pooled analyses, the tolerability profile of sugammadex was generally similar to that of placebo or neostigmine plus glycopyrrolate [12,13]. Most of the related side effects observed in phase II and III studies are non-specific, including hypotension, movement, coughing, dry mouth or nausea. Prolongation of the corrected QT interval has been described but with the same frequency as that observed in the placebo group [14]. This can be observed with several anaesthetic agents; therefore its significance is questionable. No abnormalities in laboratory parameters or changes in vital signs were considered to be related to sugammadex or of clinical significance [13].
The question of hypersensitivity to sugammadex is subject to some discussion but it is likely that the incidence is negligible. In clinical trials only one case has been confirmed in a volunteer who received a large dose. Symptoms included flushing, tachycardia and palpitations. The reaction was self-limiting and did not require any treatment. One case, following a dose of 3.2 mg/kg, was recently published. However the significance of this case is uncertain, as the subsequent skin test was performed with undiluted drug and serum tryptase levels, a marker of an anaphylactic reaction, remained within the normal range [14].

**Pharmacoeconomic considerations**

Paton published a systematic review and analysis of cost-effectiveness on the routine reversal with sugammadex when compared with a commonly used cholinesterase inhibitor. Based on UK National Health Services costs, sugammadex was calculated to be cost-effective if the value of each minute of recovery time saved was £2.40 (€3.00) [16]. Baumgart published a simulation-based analysis on the efficacy of sugammadex in an hospital with 4 operating theatres and around 4200 procedures. He was able to demonstrate an increase in additional cases by 2.4% over a 3 month period which may have a direct impact on procedural-related gross income [17].

Raft and colleagues have approached this issue in their institution where anaesthesiologists have direct access to both neostigmine and sugammadex. Dosing of sugammadex was strictly based on neuromuscular monitoring data. After one year, the total anaesthesia costs per case increased by about €6 mainly because of the substitution of neostigmine by sugammadex. However, they concluded that from a medicoeconomic point of view, this increase was counterbalanced by a faster turnover and PACU throughput [18]. It is likely that the reduction in recovery times with sugammadex might reduce the incidence of prolonged times to extubation and increase patients turn over. However, it must be highlighted that cost reductions in the operating theatre or in the PACU depends mainly on specific individual organisational factors [19].

Sugammadex is a very exciting drug because it can easily and rapidly reverse any level of rocuronium-induced neuromuscular block when given at the appropriate dose. The use of sugammadex could make anaesthesia much easier and safer. It is now obvious that the introduction of sugammadex into clinical practice has increased our therapeutic options. It is possible to reverse neuromuscular block exactly when needed. No residual paralysis should be observed in the recovery room. Based on published studies, a dose of 2.0 mg/kg sugammadex is recommended for reversing a shallow rocuronium-induce neuromuscular block. Deep rocuronium-induced block can be easily and rapidly reversed with 4 mg/kg sugammadex. This dose is not associated with recurrence of block. A dose of 16 mg/kg can efficiently and rapidly reverse rocuronium 3 minutes after its administration. However, it must be remembered that sugammadex, given in too small doses for the degree of given block, may still be sufficient to form complexes with molecules of rocuronium or vecuronium in the central vascular compartment but insufficient to sustain a redistribution of these NMBAs from the neuromuscular junction to the central compartment. The consequence of a poorly calculated dose or a relative under dosing for the specific clinical situation raises the prospect of reappearance of neuromuscular block. Therefore it is strongly recommended or possibly even mandatory to use neuromuscular monitoring (at least a single nerve stimulator) to assess the level of neuromuscular block and to determine the optimal dose of sugammadex to avoid under dosing or, possibly unnecessary overdosing in some cases.

**Key Learning points**

- Sugammadex is the first selective relaxant binding agent (SRBA) designed to reverse rocuronium and vecuronium-induced neuromuscular block.
- Sugammadex is the first agent which can reverse deep levels of neuromuscular block
- Any rocuronium-induced neuromuscular block can be easily and rapidly reversed with 2 to 3 minutes by using the appropriate dose of sugammadex
- The efficacy of non steroidal neuromuscular blocking agents remains unaffected by administration of sugammadex
- It is strongly recommended, indeed virtually mandatory to use neuromuscular monitoring (at least a single nerve stimulator) to assess the level of neuromuscular block and to determine the optimal dose of sugammadex to avoid underdosing or even overdosing.
References