SPECIAL ARTICLE

The concept behind sugammadex

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Abstract Sugammadex is the first selective relaxant binding agent. It allows rapid reversal of any degree of neuromuscular blockade induced by steroidal neuromuscular blocking agents. Sugammadex acts by encapsulation of the neuromuscular blocking agent. This prevents the drug from acting on prejunctional and postjunctional nicotinic receptors, allowing acetylcholine to activate these receptors, and resulting in reversal of the neuromuscular blockade. Objective monitoring of the degree of neuromuscular blockade is strongly recommended to determine the optimal dose of sugammadex. A good understanding of the concept behind sugammadex is essential in order to use this reversal agent in clinical practice.

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PALABRAS CLAVE
Fármacos bloqueantes neuromusculares; Rocuronio; Vecuronio; Sugammadex; Reversión; Farmacología

El concepto detrás de sugammadex

Resumen Sugammadex es el primer agente farmacológico de unión selectiva a los bloqueantes neuromusculares. Permite la reversión rápida de cualquier grado de bloqueo neuromuscular producido por agentes bloqueantes neuromusculares esteroides. Sugammadex actúa mediante la encapsulación del bloqueante neuromuscular. Esto evita la acción de dichos fármacos en los receptores nicotínicos prejuncionales y posjuncionales, permitiendo que la acetilcolina active estos receptores, lo cual resulta en la reversión del bloqueo neuromuscular. Para determinar la dosis óptima de sugammadex se recomienda encarecidamente la monitorización objetiva del grado de bloqueo neuromuscular. Un adecuado conocimiento del concepto en que se basa sugammadex es esencial para el empleo de este reversor en la práctica clínica.

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Introduction

For more than 50 years acetylcholinesterase inhibitors have been used for more than 50 years to speed up the recovery from non-depolarising neuromuscular blockade. The major disadvantage of acetylcholinesterase inhibitors is their inability to reverse profound neuromuscular blockade.

In 1997 a new concept was developed: encapsulation of steroidal neuromuscular blocking agents (NMBAs), which allows rapid recovery from any degree of neuromuscular blockade, including profound blockade. This concept led to the development of sugammadex (Bridion®), the first selective relaxant binding agent.

The aim of this overview is to explain the mechanism of action of sugammadex to enable the clinical anaesthetist to make optimal use of this reversal agent.

Molecular Interaction

One sugammadex molecule can only form a complex with one steroidal NMBA molecule. This is known as 1:1 binding. This phenomenon has been misinterpreted by the assumption that the binding between sugammadex and the neuromuscular blocking agent (NMBA) molecule is irreversible.

Based on this assumption, it has been wrongly concluded that adequate reversal could be obtained by matching the number of sugammadex molecules with an equal number of NMBA molecules. The common intubating dose of rocuronium and vecuronium is 0.6 and 0.1 mg/kg, respectively. Since the molecular weight of rocuronium bromide and vecuronium bromide is known (609.68 and 637.73), one can convert the intubating doses of these NMBAs into 984.12 and 156.81 nmol/kg, respectively. An equimolar amount of sugammadex would correspond to 2.14 and 0.34 mg/kg (molecular weight of sugammadex 2178.01). Based on these assumptions, any degree of neuromuscular blockade induced by 0.6 mg/kg rocuronium could be reversed by 2.14 mg/kg sugammadex. However, clinical studies have clearly demonstrated that higher doses of sugammadex are required to reverse profound blockade 4 mg/kg for reversal at a posttetanic count of 1-2. Furthermore, immediate reversal after a dose of 1.2 mg/kg rocuronium requires a dose of 16 mg/kg sugammadex and not 4.28 mg/kg.

Using a similar argument, it could be concluded from the intubating doses of pancuronium and vecuronium (0.1 mg/kg) that the intubating dose of rocuronium should also be 0.1 mg/kg (the molecular weights of these steroidal NMBAs are similar). There is more than sufficient clinical evidence showing that such a low dose rocuronium is insufficient to achieve appropriate intubating conditions.

Therefore, it is clear that dose calculations should not be based on the assumption that the interaction between sugammadex and the steroidal NMBA is irreversible.

Affinity

The interaction between sugammadex and steroidal NMBAs is reversible. In other words, complexes are formed (association), but complexes also fall apart (dissociation). High affinity binding is characterised by a high association rate and a low dissociation rate. The ratio between the association rate and dissociation rate at equilibrium is known as the association equilibrium constant (K_a), which describes the affinity between two molecules in steady state.

The K_a values of sugammadex for rocuronium and vecuronium are 25.10^6 and 10.10^6 M^-1, respectively, indicating that rocuronium has a higher affinity for sugammadex than vecuronium.

The degree of complexation is mainly determined by three factors: 1) the concentration of the NMBA, 2) the concentration of sugammadex, and 3) the association equilibrium constant.

The degree of complexation between rocuronium and sugammadex can be calculated. Figure 1 shows the degree of complexation when equal concentrations of steroidal NMBAs and sugammadex are interacting with each other. To obtain higher degrees of complexation, the concentration of sugammadex has to exceed the concentration of rocuronium.

This becomes clear when one observes the changes in plasma concentration of rocuronium and sugammadex, when 2 mg/kg of sugammadex is administered on reappearance of the second twitch (T2) of the TOF response. The concentration of sugammadex clearly exceeds the rocuronium concentration, which will ensure that the majority of rocuronium molecules are complexed with sugammadex (Figure 2).
Based on these plasma concentrations, one can also calculate the ratio between the total plasma concentration of rocuronium and sugammadex and the concentration of free rocuronium (not bound to sugammadex) as shown in Figure 3. The plasma concentration of free rocuronium is initially extremely low, but slowly rises during the first 30 min (please note that the concentration in Figure 3 is shown in nM and not in μM; nanomolar concentrations do not cause neuromuscular blockade). The sugammadex/rocuronium ratio initially exceeds a value of 6, then stabilises after 30 min to a value of 2.

Concentration gradients and speed of reversal

Since the plasma concentration of sugammadex after a recommended dose of this reversal agent exceeds that of the steroidal NMBA, the excess of unbound sugammadex molecules in plasma will rapidly leave the bloodstream and enter the extracellular space. At the same time, the concentration of the unbound steroidal NMBA in plasma will be close to zero, creating a NMBA concentration gradient between extracellular fluid and plasma, resulting in a rapid movement of the steroidal NMBA towards the bloodstream. These two opposing movements contribute to the rapid encapsulation of the NMBA molecules, resulting in rapid reversal of neuromuscular blockade.

Postjunctival Effects

Occupation of the postjunctival nicotinic receptors does not immediately result in neuromuscular blockade. At least 75% of the nicotinic receptors have to be occupied by a non-depolarising NMBA before the first signs of neuromuscular blockade will become apparent. This margin of safety has been described in anaesthesia as the "iceberg effect", and in pharmacology as "non-linear occupation-effect relationship". After administration of sugammadex, the NMBA molecules that are not bound to the nicotinic receptor will be encapsulated first. This will cause rocuronium molecules, which are still bound to the nicotinic receptor, to free themselves and become available for encapsulation by sugammadex. Once 25% of the postjunctional receptors have been freed, acetylcholine will be able to act again on this fraction of the receptors and restore muscle contraction.

Prejunctival Effects

Activation of prejunctival nicotinic receptors by acetylcholine facilitates the release of acetylcholine in subsequent nerve stimuli. Occupation of the prejunctival receptors by non-depolarising NMBAs reduces this effect of acetylcholine, resulting in TOF fade. When a slow infusion of non-depolarising NMBAs is started, the first phenomenon one observes is TOF fade. During recovery, the last sign of neuromuscular blockade to disappear is TOF-fade. This suggests that non-depolarising NMBAs are more potent at prejunctival nicotinic receptors than at postjunctival receptors. However, studies with human nicotinic receptors expressed in frog oocytes have shown the opposite. This raises the hypothesis that prejunctival nicotinic receptors also show a non-linear occupation-effect relationship, but this relationship is the opposite of that of the postjunctival nicotinic receptors. Occupation of a very small fraction of prejunctival nicotinic receptors might already cause complete blockade of the facilitatory effect of acetylcholine at NMBA concentrations that do not affect postjunctival nicotinic receptors.

Administration of sugammadex will also result in a rapid liberation of the prejunctival nicotinic receptor occupation by the NMBA. This will restore the facilitatory effect of acetylcholine on its own release, which will further contribute to the speed of reversal.

Reversal after sugammadex depends on acetylcholine

It is important to realise that sugammadex, by itself, does not cause reversal. Sugammadex will only reduce the NMBA occupation of the pre- and post-junctival nicotinic receptors. It is acetylcholine that causes reversal. Therefore, sugammadex will not cause reversal in the absence of motor nerve activity or acetylcholine release. When the administration of a recommended dose of sugammadex does not result in adequate reversal, one should consider whether a lack of acetylcholine release is the causative factor (hypermagnesaemia, hypocalcaemia, antibodies against pre- and/or postjunctival nicotinic receptors etc.)

Recommended dose of sugammadex

Based on the margin of safety of the postjunctival nicotinic receptor system, one could argue that it is not required to encapsulate the majority of steroidal NMBA molecules. Once the occupation of the postjunctival nicotinic receptors by the NMBA is reduced to 75%, the muscle function should be restored. However, after complete recovery of the first twitch (T1) of the TOF response, T4 might still be depressed, indicating that the prejunctival nicotinic receptor function is not restored yet. In the past, a TOF ratio of 0.7 was the standard, but more recently, a TOF ratio of 0.9 has become the gold standard.
Unfortunately, research groups that had the facilities to measure NMBA plasma levels have focussed on pharmacokinetic studies with blood sampling at fixed time intervals, whereas research groups focussing on neuromuscular monitoring have not measured plasma levels of NMBA during different phases of recovery. As a result, there is still insufficient information regarding plasma levels of NMBA at different Post-Tetanic Counts, re-appearance of T1, T2, T3 and T4, and different degrees of TOF recovery.

Two small studies have reported a plasma level of ~1.0 μM rocuronium at recovery of the TOF ratio to 0.75, so one can estimate that the plasma level of rocuronium at a TOF ratio of 0.9 will be approximately 0.85 μM. For vecuronium the situation is more complicated since, in contrast to rocuronium, this NMBA is metabolised and the metabolites can be found in plasma. The metabolites are less potent NMBA than vecuronium, but can also form complexes with sugammadex.

To reduce the plasma level of rocuronium from 1.90 μM (concentration at re-appearance of T2) to 0.85 μM (estimated concentration at TOF ratio 0.9), one can calculate that a minimum concentration of 1.17 μM of sugammadex would be sufficient. However, this would create a very small concentration gradient between extracellular concentration and plasma concentration. As a result, recovery would be very slow. Furthermore, any decrease in acetylcholine release would be followed immediately by re-occurrence of neuromuscular blockade. Therefore clinical studies (using either intravenous or inhalation anaesthesia) have been used to determine the doses of sugammadex that provide fast (within 3 min) and maintained reversal of neuromuscular blockade (TOF ratio > 0.9). This formed the basis for the dose recommendations.

Risk of Displacement

Recommended doses of sugammadex not only provide rapid and maintained reversal of neuromuscular blockade, but also reduce the risk of displacement. Other drugs with affinity for sugammadex can displace the steroidal NMBA from its complex with sugammadex, which can lead to re-occurrence of neuromuscular blockade. During the development of sugammadex, experimental compounds have been synthesised with very high affinity for sugammadex, but lacking neuromuscular blocking activity.

After successful reversal of rocuronium- or vecuronium-induced neuromuscular blockade, these agents caused displacement of the steroidal NMBA and re-occurrence of neuromuscular blockade. The degree of re-occurrence of blockade in in-vitro and in-vivo animal experiments was in good agreement with the predicted displacement of the NMBA. This led to the development of a pharmacokinetic-pharmacodynamic model to predict the risk of displacement.

This model uses a worst-case scenario model: the model assumes that drugs do not have affinity, receptors do not bind to proteins, and drugs do not enter cells. Therefore, this model tends to overestimate potential risk. However, this has the advantage that potential changes in acetylcholine release (the driving factor in reversal) are compensated.

In a simple model (container with fixed volume), one can use the total plasma concentration of rocuronium and sugammadex observed after 5, 15, and 30 min (see Figure 2) and calculate the concentration a drug with a certain affinity for sugammadex that will cause displacement resulting in a free rocuronium plasma level 1.0 μM, which has been linked to a TOF ratio of 0.7 in the past. The results of these calculations are shown in Figure 4.

When the affinity of a drug is known, one can look up at which drug concentration the free rocuronium concentration will reach a value of 1.0 μM. Five minutes after administration of sugammadex, a higher drug concentration is required than after 30 min. It also becomes clear that at a low concentration of a drug, no relevant displacement will take place, even for drugs with high affinity for sugammadex. Similarly, compounds with low affinity will require higher than therapeutic concentrations to cause displacement.

However, when lower than recommended doses of sugammadex are administered, the curves in Figure 4 will move to the left and downward. As a result, lower concentrations of certain drugs will cause displacement with its associated clinical risk.

Due to its lower affinity for sugammadex, vecuronium will be more prone to be displaced from its complex with sugammadex. However, when the dose recommendations for sugammadex are followed, the excess of sugammadex will be greater, since vecuronium is a more potent NMBA with a lower plasma concentration. Any displaced vecuronium molecule is therefore more likely to be recaptured by sugammadex molecules.

Conclusion

Sugammadex allows the anaesthetist to rapidly and effectively reverse rocuronium- or vecuronium-induced neuromuscular blockade at any time point after administration. Using the recommended doses, one can obtain fast and maintained reversal of neuromuscular blockade with a very
low risk of re-occurrence of blockade. Since the dose of sugammadex depends on the depth of blockade, objective neuromuscular monitoring is strongly recommended. Monitoring not only helps in the determination of the optimal dose of sugammadex, but it also demonstrates whether reversal is effective (TOF ratio $>0.9)$. At present, the following dose recommendations for sugammadex are available: 2 mg/kg for reversal on re-appearance of the second twitch of the TOF response, 4 mg/kg for reversal at a post-tetanic count (PTC) 1·2, and 16 mg/kg sugammadex for immediate reversal after 1.2 mg/kg rocuronium. Future studies might determine the level of neuromuscular blockade that can be reliably reversed with doses of sugammadex between 2 and 4 mg/kg.

Conflict of Interest

Both authors are former employees of Merck Sharp & Dohme (MSD). This overview reflects their personal opinion.

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