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Sugammadex: the First Selective Relaxant Binding Agent for Reversal of Neuromuscular Block

Since the introduction of tubocurarine as neuromuscular blocking agent in 1944, the pharmaceutical industry has made a large effort to develop non-depolarising muscle relaxants with fast onset, short duration of action and lack of cardiovascular and pulmonary side-effects. However, the development of agents for the reversal of neuromuscular block has been very limited. Traditionally, inhibitors of acetylcholinesterase are being used (neostigmine, pyridostigmine, edrophonium), often in combination with a muscarinic antagonist (atropine, glycopyrrolate). However, this approach is only effective when the spontaneous recovery from neuromuscular block has started. In the period between injection of the neuromuscular blocking agent and the start of spontaneous recovery, no agent is currently available for the effective reversal of block.

During *in-vitro* tissue bath experiments in 1997, it was discovered that steroidal neuromuscular blocking agents (rocuronium, vecuronium) could be dissolved using cyclodextrins. The hydrophobic steroidal part of these agents enters the cavity of the cyclodextrin, increasing the water solubility of the neuromuscular blocker. During these experiments, the idea was born to modify cyclodextrins in such a way that they completely encapsulate the blocker molecule. As a result, the steroidal neuromuscular blocking agent could be prevented from acting on nicotinic receptors and instantaneous reversal of block could be expected. This hypothesis triggered the synthesis of a large number of modified cyclodextrins, followed by extensive *in-vitro* and *in-vivo* pharmacological studies. This resulted in the discovery of sugammadex (Org 25969), the first example of a selective relaxant binding agent; a new type of reversal agent. Intravenous administration of sugammadex causes a rapid complexation of rocuronium molecules in blood. This creates a concentration gradient between tissue and blood. As a result, rocuronium molecules move rapidly back to the circulation where they are captured by other empty sugammadex molecules. At a later stage, sugammadex also leaves the circulation and starts to encapsulate even more rocuronium molecules in the tissues. These processes will cause a rapid inactivation of rocuronium and, indeed, studies in human volunteers have shown that complete recovery from rocuronium-induced neuromuscular block can be obtained within 3 min (the spontaneous recovery time is ~50 min). Phase II studies demonstrated that even very profound block can be reversed rapidly.

Sugammadex also proves to be effective against vecuronium-induced neuromuscular block, but, because of its structure and mechanism of action, is ineffective against non-steroidal neuromuscular blocking agents like atracurium, mivacurium, and succinylcholine. The reversal by sugammadex is independent of the type of anaesthetic agent used during the surgical procedure. Sugammadex is excreted via the kidneys and our studies have shown that the renal excretion of rocuronium is markedly increased after sugammadex administration. Phase III clinical trials are presently running in both the USA and Europe. A successful completion of these studies might, after more than sixty years, finally give the anaesthesiologists full control over neuromuscular block.