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New Developments in Neuromuscular Blockade

Calgary - After a period of relative inactivity, there is currently an upsurge in the research and development of promising new compounds for anesthesiology. This work touches on all the major therapeutic categories associated with this specialty, including hypnotics, where multiple alternative formulations of propofol are under development, and analgesics, where research encompasses opioids, other centrally acting drugs and peripherally acting drugs. Regarding muscle relaxants, much research is focused on the development of reversal agents for the management of neuromuscular blockade. Work in this field is led by ongoing clinical evaluation of sugammadex, a cyclodextrin that binds rocuronium and rapidly and completely reverses neuromuscular blockade. Its potential clinical applications range from variable-length surgical procedures to succinylcholine replacement to a possible therapeutic role in certain neuromuscular disorders.

The clinical practice of neuromuscular blockade dates to 1942 with the first reported clinical use of curare in general anesthesia (*Anesthesiology* 1942;3:418-20). Anesthesiology researchers have since sought to improve the practice of neuromuscular blockade by developing compounds that offer better efficacy and a lower risk of complications, particularly problems related to residual block.

Counteracting the Ceiling Effect and Improving Recovery Time

Recently, the use of reversal agents has attracted considerable attention due to the simple fact that they work; they accelerate reversal of neuromuscular blockade in all circumstances, stated Dr. François Donati, *Hôpital Maisonneuve-Rosemont*, and Professor of Anesthesiology, *Université de Montréal*, Quebec. "However, the currently available reversal agents have a ceiling effect: they take time to work and they have side effects."

The traditional criterion for reversal of neuromuscular block has been a train-of-four (TOF) >0.7 . However, evidence suggests that a TOF $>70\%$ is associated with incomplete recovery (*Anesthesiology* 1997;86:765-71) and that a more appropriate criterion for full recovery may be a TOF >0.9 (*Anesthesiology* 1997;87:1035-43).

Currently, acetylcholinesterase inhibitors are the only available reversal agents. As the agents inhibit acetylcholinesterase, less acetylcholine is broken down, leading to increased competition with the non-depolarizing muscle relaxant (e.g. atracurium, mivacurium, vecuronium), explained Dr. Donati. At 100% inhibition, a ceiling effect is encountered. In clinical practice, the ceiling effect is not measured because an agent eventually disappears from the body, and some type of spontaneous recovery occurs, Dr. Donati continued. Concern about reversal relates to how long it takes for spontaneous recovery to occur. A deeper block necessarily leads to a longer recovery time.

Administration of neostigmine can speed up the recovery process compared to spontaneous recovery. However, typical doses used in clinical practice are close to the ceiling effect, noted Dr. Donati, and even at maximum doses, recovery will still take a fairly long time in the setting of deep neuromuscular blockade.

Timing of neostigmine administration poses additional concerns related to a clinician's ability to detect residual blockade. This was first demonstrated almost 20 years ago in a comparison of double-burst stimulation (DBS) and conventional TOF evaluation to determine residual blockade in patients undergoing surgery (*Anesthesiology* 1989;70:578-81). The results showed that absence of fade with TOF was associated with a 48% likelihood of significant residual blockade compared to 9% with DBS.

"At a TOF ratio above 40%, virtually no one recognized the presence of significant residual blockade," Dr. Donati related to listeners. "Between 0.4 and 0.9, you have no way of telling, by use of visual or tactile senses, whether a patient is paralyzed. You can have a long period of time when you don't know whether your patient has recovered." He added that in patients receiving halogenated agents, their discontinuation does not substantively affect the recovery time.

Safety Considerations

Conventional reversal agents such as neostigmine also have cardiovascular effects that include increased heart rate and prolongation of the QTc interval. These effects are well recognized within the anesthesia community and generally are no reason for concern. Still, the effects should be kept in mind with respect to their potential impact on an individual patient, Dr. Donati remarked. As an alternative to neostigmine for reversal, edrophonium works faster and requires less atropine. However, the agent is less effective for reversal of deep block.

On average, heart rate remains stable with edrophonium, but increases and decreases can occur, and cardiac arrhythmias have been reported in some patients.

Overall, the currently available reversal agents improve neuromuscular transmission in all circumstances, Dr. Donati concluded. They appear to achieve optimum efficacy at first-twitch (T1) recovery of 25%, and they reduce the likelihood of residual paralysis. However, considerable room for improvement remains with respect to reversal of deep blockade, rapidity of reversal and side effects.

Exploring the Armamentarium

There is a need for better reversal agents and muscle relaxants. The “ideal” muscle relaxant would possess certain characteristics, according to Dr. Scott Groudine, Professor of Anesthesiology, Albany Medical College, New York: rapid onset; flexible (controllable) duration of action; no clinically relevant histamine release or other effects; low cost; easy storage; no significant drug interactions; and utility in all types of patients, including those with renal or hepatic failure

Succinylcholine has a rapid onset of action and is inexpensive, but is associated with significant adverse effects and has a mortality risk, noted Dr. Groudine. In general, the available non-depolarizing agents have a slow onset and offset of action. The one exception is rocuronium, which has a rapid onset—depending on dose—and an offset that depends on dose, timing and use of reversal agents.

New-generation muscle relaxants include gantacurium, the first of a new class of isoquinolines. It has a rapid onset, short duration of action and can be reversed by edrophonium or cysteine from any depth of block. Its efficacy does not appear to be influenced by the type of general anesthetic regimen used. With respect to metabolism, gantacurium elimination is not enzyme- or organ-dependent. It does have adverse effects that include increased heart rate, hypotension and an association with histamine release (*Anesthesiology* 2004;100:768-73).

New-generation Reversal Agents

An optimal reversal agent would offer another approach to improved management of neuromuscular blockade. According to Dr. Steven Shafer, Professor of Anesthesia, Stanford University, Palo Alto, California, sugammadex has emerged as the leading candidate for that role. As the first selective relaxant binding agent, it has a pocket designed specifically to bind rocuronium. In binding available rocuronium, it rapidly

and completely reverses neuromuscular blockade, even in the presence of ongoing rocuronium infusion. Initial clinical testing demonstrated that sugammadex 8 mg/kg reversed neuromuscular blockade within one minute and caused no apparent toxicity (*Anesthesiology* 2005; 103:695-703, *Anesthesiology* 2006;104:667-74). “If sugammadex does not have some as-yet unrecognized toxicity, it will render conventional pharmacologic reversal of neuromuscular blockade obsolete,” remarked Dr. Shafer. “Patients will no longer be exposed to the nausea-inducing properties of neostigmine or the tachycardic effects of atropine and glycopyrrolate.”

Dr. Groudine told delegates that the agent can be administered any time after rocuronium, it can reverse any depth of neuromuscular blockade, and its efficacy does not appear to be influenced by the general anesthetic regimen.

Under usual clinical circumstances, rocuronium reversal takes longer with maintenance inhalational anesthesia than with propofol. Clinical evaluation of sugammadex revealed no difference in recovery to TOF >0.9 whether sevoflurane or propofol was used (*Anesth Analg* 2007;104:563-8). “Administration of sugammadex in a blocked patient leads to rapid encapsulation of rocuronium,” indicated Dr. Groudine. “It removes rocuronium from its site of action, leading to complete reversal of neuromuscular blockade. The inactive complex formed by the binding of sugammadex to rocuronium is then excreted by the kidneys.” He told delegates, “We have seen recovery within two or three minutes after administration, and that’s full recovery, not just partial.”

Dr. Groudine explained that with sugammadex reversal, rocuronium’s route of elimination can be changed. Rocuronium is primarily excreted hepatically, and only 14% is recovered in urine. In contrast, sugammadex is predominately excreted by the kidneys. The literature indicates that when sugammadex is given to a rocuronium-treated patient, 39% to 68% of the rocuronium is recovered in urine (*Anesthesiology* 2005; 103:695-703).

The novel agent would appear to be well suited for surgeries that have a variable or unpredictable length, such as a foreign body in the airway, esophageal dilation, diagnostic laparoscopy, ocular trauma, or cancer resection. It also has clear utility in motor nerve monitoring associated with parotid and facial nerve surgery, breast surgery or spinal surgery, Dr. Groudine suggested.

Other potential applications include succinylcholine replacement, emergency room and neurosurgical evaluation after intubation with paralytics in the field, and deep relaxation for surgical closure. Dr. Groudine offered that it might even have a role in the management of certain neuromuscular disorders, such as myasthenia. □

Note: At the time of printing, sugammadex is not approved in Canada.

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