Research Review
SPEAKER SERIES

Innovation in anaesthesia and NBA management - April 2011

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Professor Meistelman is Medical Director and Manager of the Department of Anaesthesia and Critical Care at Brabois University Hospital, Vandoeuvre, France. He has significant clinical experience in multidisciplinary adult anaesthesia including transplantation and paediatric anaesthesia, and in perioperative critical care medicine.

Prof. Meistelman is Vice-Editor-in-chief, Annales Française d'Anesthésie-Réanimation and reviewer of scientific articles for several scientific journals including Anaesthesiology, Anaesthesia Analgesia, Acta Anaesthesiologica Scandinavica and the British Journal of Anaesthesia.

Prof. Meistelman is well published and has approximately 85 publications in peer-reviewed journals. He has presented at more than 150 invited lectures, both nationally and internationally (including the European Society of Anaesthesiology and the Postgraduate Assembly in Anesthesiology), on various topics including neuromuscular blocking agents, pharmacology in paediatrics, analgesia and sedation in the ICU.

This publication is a summary of a presentation by Professor Claude Meistelman, Medical Director and Manager of the Department of Anaesthesia and Critical Care at Brabois University Hospital, Vandoeuvre, France. Prof. Meistelman spoke in Auckland and Wellington in April 2011 about innovation in anaesthesia and the unmet needs of neuromuscular-blocking agent management.

Innovation: from general health care to operating room

Drug development and approval

In the past it was possible to use medicines without approval from an Institutional Review Board and without fully understanding a drugs mechanism of action. The poison curare has been used for hundreds of years, however, its mechanism of action was only determined in 1850. Although Cullen and Rovenstine, prominent anaesthetists in the mid 20th century, considered the agent too dangerous for clinical use, Griffith and Johnson in 1942 successfully used the agent in humans.[1] Use of this agent and others preceded the creation of the Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) and their stringent approvals process.

In the 21st century it has become increasingly difficult to have drugs approved for humans use. Only 20 to 25 new drugs are approved every year and, in anaesthesia, only one drug (sugammadex [Bridion]) has been approved in the last 10 years.

For every 5000 to 10,000 potential medicinal compounds discovered, only one will become an FDA-approved drug (see **Figure 1**).[2] Furthermore, the process from discovery to approval takes approximately 10 to 15 years.[2] Pharmaceutical innovation is becoming an increasing challenge and, despite increased spending in research and development, the number of drug approvals continues to decline.[3]

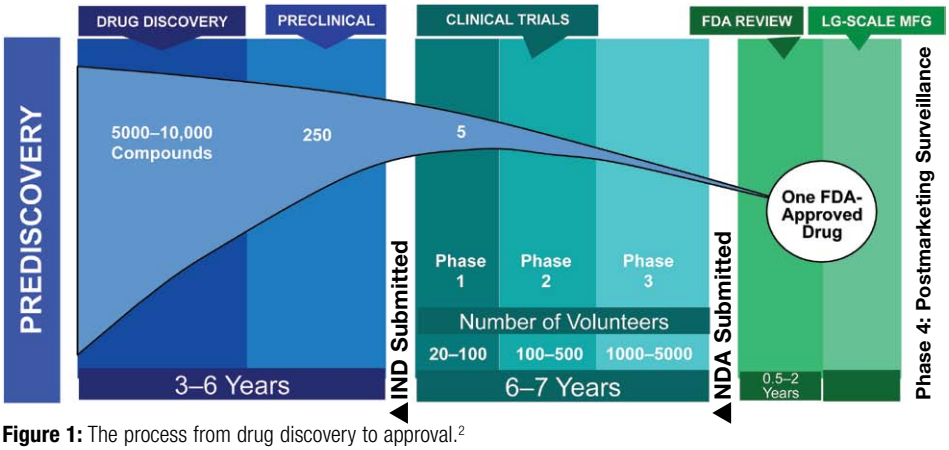


Figure 1: The process from drug discovery to approval.[2]

FDA = Food and Drug Administration; IND = investigational new drug; LG-Scale MFG = large-scale manufacturing; NDA = new drug application

Are medical innovations worth it for humans?

An article on history's greatest innovations by Keeley in 2007 lists anaesthetics and surgery, vaccines and antibiotics, and genetic sequencing amongst the most invaluable innovations ever.[4] Such innovations have saved lives, extended average life span and/or improved quality of life.

With regard to anaesthesia, the question arises as to whether innovations always improve patient safety, comfort and outcomes?

Prof. Meistelman says that we are often too focused on evidence-based medicine and that in some cases results have been misleading. He sites the research of Beecher and Todd who, in 1954, published data from their detailed study of approximately 600,000 surgical cases, concluding that the use of muscle relaxants causes a 6-fold increase in anaesthesia-related deaths and that such agents should be avoided.[5] It has, however, become evident over the last 50 years that when used properly, the advantages of neuromuscular-blocking agents (NMBAs) far outweigh their disadvantages. Surprisingly, there is only one randomised controlled trial (RCT) showing the benefit of neuromuscular block during abdominal surgery.[6]

Prof. Meistelman says that while evidence based medicine is important, not all interventions require RCTs to demonstrate their advantages. Smith and Pell cleverly made this point in their paper on parachute use for the prevention of death.[7] They pointed out that while there have been no RCTs investigating the benefit of such intervention, observational analysis clearly shows it is advantageous. They concluded that medicine might benefit if individuals

who insist on evidence-based medicine organised and participated in a double-blind, randomised, placebo controlled, crossover trial of the parachute. Following the publication of Smith and Pell's paper, there was a flurry of publications supporting the idea that in some cases, if the science is good, intervention should be initiated before the trials are undertaken. One such paper by Potts et al outlined the following interventions to show how overemphasis on RCTs in certain settings would have incurred avoidable deaths; oral rehydration therapy in childhood diarrhoea, male circumcision in human immunodeficiency virus, misoprostol for postpartum haemorrhage.[8]

Improvements for the patient – anaesthetics

The use of neuromuscular-blocking agents (NMBAs) represents one of the most important advances in anaesthesiology and it was obvious without RCTs that patients benefit from the use of NMBAs during abdominal and gynaecological surgery. However, if medicine had trusted the findings of Beecher and Todd, then the use of NMBAs would have been discontinued.[5] Fortunately, it was discovered that the increase in mortality shown by Beecher and Todd could be reduced by the appropriate use of such agents. Namely, the correct dose and timing of administration, the use of controlled perioperative ventilation and the reversal of neuromuscular block at the end of surgery. In fact, the use of neostigmine for reversal of neuromuscular block is a good example for the lack of need for evidence-based medicine in some cases. In the early 1950s, T. Cecil Gray always reversed neuromuscular block with neostigmine, and realised the error of not doing so as reported by Beecher and Todd.[5] Gray routinely used neostigmine 5 mg following d-tubocurarine 45 mg, and neostigmine 2.5 mg following atracurium or vecuronium. This use was not based on data from RCTS, but rather upon observation.

An analysis of anaesthetic mortality in France during two time periods (1978-82 and 1996-99) has shown a 10-fold decrease in death rate over time.[9] The decreased mortality rate was not due to a single factor, but rather appears to be due to several factors. Innovations in anaesthesia in the last 20 years that have contributed to a decline in mortality rate include the mandatory use of the recovery room (eliminating the risk of hypoxia during recovery), the development of perioperative monitoring (FiO_2, SpO_2, capnography, halogenated agents, temperature assessment, neuromuscular transmission monitoring etc.), new drugs with fewer cumulative side effects, and a focus on the potential for anaesthesia to affect perioperative outcomes.

Do all innovations improve patient safety and outcomes?

Bispectral index (BIS) monitoring

BIS monitoring is widely used in North America to prevent perioperative awareness. In 2003, the FDA produced the following statement regarding its use: *`BIS may be used as an aid in monitoring the effects of certain anaesthetic agents. Use of BIS monitoring... may be associated with the reduction of the incidence of awareness with recall in adults during GA'*. This statement was released in the absence of supportive studies. In 2008, a group of researchers published a paper explaining that, according to their investigations, anaesthesia awareness occurred even when BIS values were within target ranges.[10] They concluded that their data did not support the routine use of BIS monitoring as part of standard practice.

Robot-assisted surgery

Researchers recently reported findings indicating that robot-assisted surgery may not improve patient outcomes or quality of life.[11] They reported that while some short-term benefits exist, the cost of such technology incurs an additional cost of approximately $1600 per procedure. They reported that robot systems are expensive ($1 million to $2.5 million) and that observational evidence fails to show that the long-term outcomes of robot-assisted surgery are superior to those of conventional surgery; there are currently no large-scale RCTs indicating the benefit of this technology.

New drugs

There is substantial evidence that new medicines have improved patient outcomes. Lichtenberg et al investigated the impact of new drug launches on longevity in their longitudinal study involving data from 52 countries.[12] They estimated that new drugs have accounted for 0.79 years (40%) of the 1986-2000 increase in longevity (see **Figure 2**).

Fast-track surgery

Fast-track surgery has resulted in significant gains. This intervention reduces the length of hospitalisation, results in better patient outcomes, increases the number of patients being treated and reduces the level of resources required.

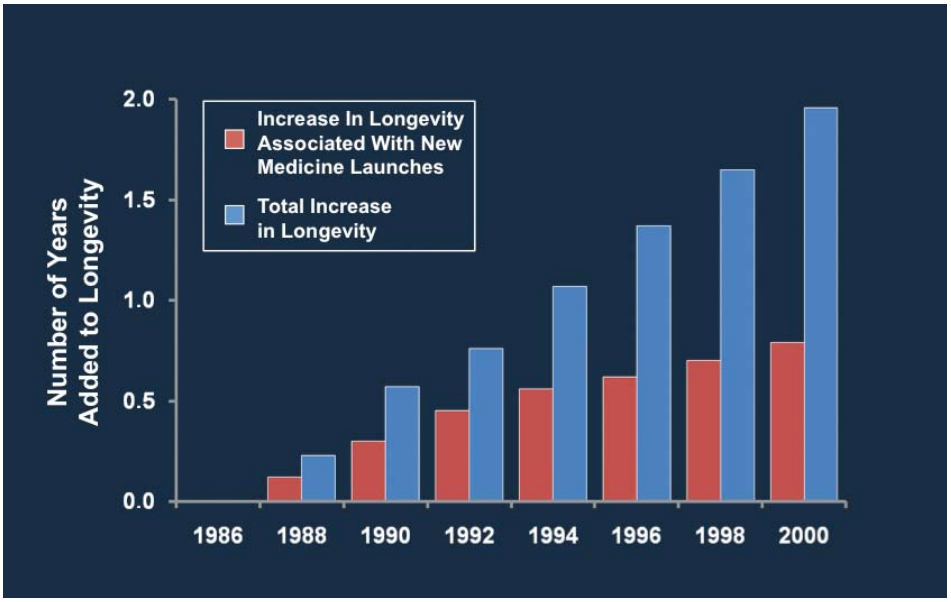


Figure 2: The impact of new medicine launches on longevity. Data from 52 countries from the period 1986 to 2000.[12]

More attention to value-enhancing innovations is required

Innovations in medicine clearly saves lives. However, despite the widespread adoption of surgical tools, there is often a lack of outcomes data to justify their cost-benefit ratio. Often the maintenance of such tools is costly. In comparison, anaesthesia-related costs are incredibly low during surgical procedures, even during complicated procedures. Prof. Meistelman says that drug costs must be considered in the context of their clinical value.

Are deep levels of neuromuscular block required?

Prof. Meistelman and colleagues have shown that a 0.5 mg/kg dose of rocuronium will induce a more intense level of block at the adductor pollicis muscle than at the adductor muscles of the larynx (see **Figure 3**).[13] However, the onset of muscle block and recovery are faster at the laryngeal adductor muscles.

While it is possible to successfully intubate a patient without the use of a NMBA, there is clear evidence that doing so can lead to laryngeal and/or pharyngeal trauma. A study by Kambic and Radsel in 1978 investigating patients who had been intubated without NMBAs, showed that severe lesions occurred in 6.2% of patients, haematoma of the vocal cords occurred in 4.5%, supraglottic haematoma in 0.7% and laceration of the vocal cords in 0.9%.[14] Peppard and Dickens showed similar findings, with 4.6% of their subjects developing haematoma of the vocal cords.[15]

Mencke and colleagues demonstrated that the use of a NMBA can significantly reduce the incidence of vocal cord lesions following intubation. In their study, they compared the vocal cords of 73 patients who had been randomly assigned to receive a propofol-fentanyl induction regimen with or without atracurium.[16] Vocal cord sequelae occurred in 15/36 placebo recipients compared with only 3/37 atracurium recipients ($p = 0.002$). A similar finding was found with regard to postoperative hoarseness. Another study showed that the use of the NMBA rocuronium was associated with a better Cormack and Lehane class during intubation and with fewer attempts required for successful intubation compared with placebo.[17] Prof. Meistelman says that there is a clear need for the use of a NMBA during induction.

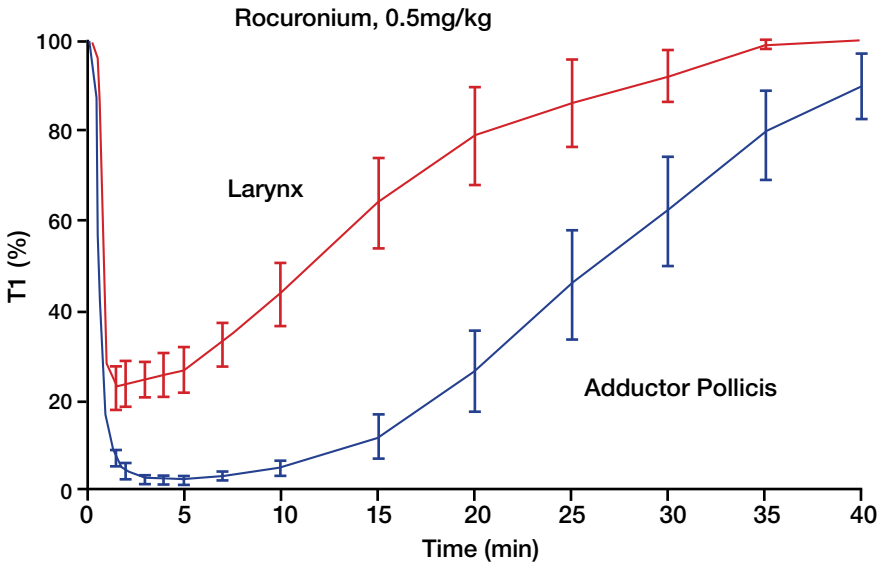


Figure 3: First twitch height (T1) as a percentage of control, versus time after injection of rocuronium 0.5 mg/kg.[13]

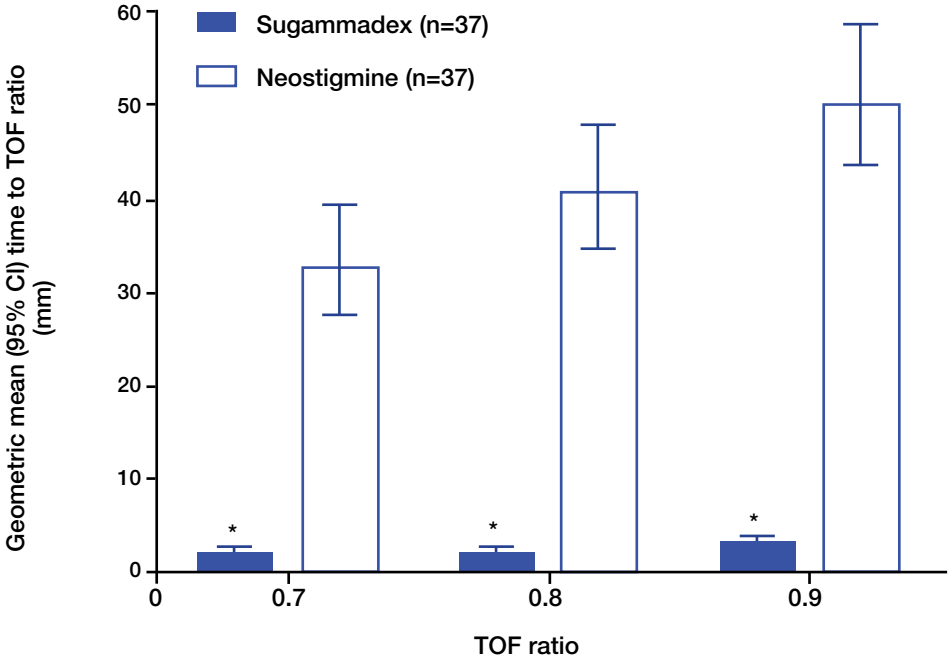


Figure 4: Time from start of administration of sugammadex or neostigmine to recovery of the train-of-four (TOF) ratio to 0.7, 0.8 and 0.9.[24]

* $p < 0.0001$ vs neostigmine

NMBAs during surgery

Paralysis of the diaphragm and the rectus abdominis muscles is required during opening of and closure of the peritoneum. Non-depolarising muscle relaxants prevent extrusion of the abdominal contents and the occurrence of hiccups. The diaphragm is more resistant to the effects of an NMBA than the adductor pollicis muscle and recovers before the adductor pollicis. This explains why sometimes an anaesthetist may be monitoring the patient and sees no response to stimulus of the adductor pollicis, but the surgeon is complaining. Compared with the adductor pollicis, the abdominal wall muscles are also more resistant to the effects of a NMBA and recover more quickly.[18]

The use of a NMBA was found to significantly improve surgical conditions in a study by King et al, who assessed surgical field rating during radical prostatectomy in patients randomised to receive vecuronium (n = 59) or placebo (n = 61).[19] These researchers found that while 62.3% of placebo recipients had surgical field ratings of good to excellent, 88.1% of vecuronium recipients had such a rating.

Another interesting study showing advantages with the use NMBAs, was that by a French group investigating the prevalence of erectile dysfunction after intramedullary femoral nailing.[20] They found that the group of patients with no erectile dysfunction had received a higher induction dose of curare than those who exhibited erectile dysfunction (5.4 mg vs 3.6 mg; p = 0.03). They concluded that higher levels of curare resulted in optimal relaxation and reduced pressure on the pudendal nerves by the perineal post.

Reversing deep block

Arbous et al in their large cohort study investigating the impact of anaesthesia management on morbidity and mortality reported that the reversal of neuromuscular block was associated with a significantly reduced risk of 24-hour postoperative mortality and coma, for both the reversal of muscle relaxants and the combination of muscle relaxants and opiates (unadjusted ORs 0.236 [95% CI 0.102-0.547] and 0.220 [0.158-0.306]).[21]

The question arises as to whether we need to reverse patients at the end of the case with a single dose of a NMBA with intermediate duration of action, such as atracurium, rocuronium, or vecuronium. Debaene et al, measuring the Train-of-Four (TOF) ratio at the adductor pollicis, have shown that after a single dose of intermediate-duration NMBA and no reversal, residual paralysis is common, and that this may be apparent more than 2 hours after the administration of the agent.[22] In fact, two or more hours after the administration of the NMBA, 37% of patients had a TOF ratio <0.9. Prof. Meistelman explains that the last muscles to recover from a NMBA are the upper airway muscles and therefore the gold standard for the TOF ratio at the adductor pollicis is 0.9.

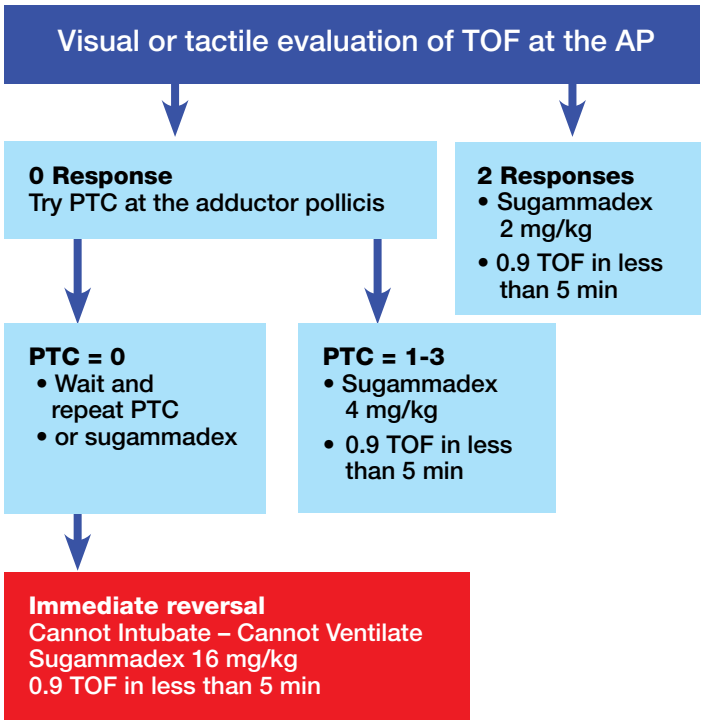
Prof Meistelman says neostigmine is widely used in Europe for the reversal of neuromuscular block. In order to use the agent efficiently, it should be administered when spontaneous recovery has already started. Kopman and colleagues have demonstrated that when neostigmine 0.05 mg/kg is given at a TOF count of 2 following cisatracurium or rocuronium, it may take 30 minutes or longer to achieve a TOF ratio ≥0.90 (28/30 cisatracurium recipients and 25/30 rocuronium recipients had a TOF ratio ≥0.90 at 30 minutes postreversal).[23]

Sugammadex vs neostigmine

A recent phase III study, comparing the efficacy of sugammadex with that of neostigmine for the reversal of rocuronium-induced deep neuromuscular block was undertaken by Jones et al.[24] In their study, patients were randomised to reversal with sugammadex 4 mg/kg (n = 37) or neostigmine 70 µg/kg. Their study revealed that the mean time from administration of study drug to recovery of TOF ratio to 0.7, 0.8 and 0.9 was significantly shorter in the sugammadex group than in the neostigmine group (see **Figure 4**). In fact, the median time to recovery of the TOF ratio to 0.9 was 2.7 minutes for the sugammadex group and 49 minutes in the neostigmine group (interquartile ranges 2.1-4.1 minutes and 35.7-65.6 minutes).

The use of sugammadex

Prof. Meistelman presents the following algorithm to outline the way in which he uses sugammadex in his patients.



AP = adductor pollicis; PTC = post-tetanic count; TOF = Train-of-Four

Selected indications for sugammadex

- Deep block during surgery
- Obese patients
- Unanticipated duration of surgery
- Respiratory disorder/obstructive sleep apnoea
- ENT endoscopies, surgery and bronchoscopies
- Expected difficult airway
- Succinylcholine contraindicated
- Emergency cases.

Cost analysis of sugammadex use

Prof. Meistelman and colleagues have analysed the financial cost of using sugammadex for cancer patients at their institution. Sugammadex comes in 2 and 5 mL vials (100 mg/mL) and a single 2 mL vial is used when giving a dose of 2 mg/kg in a patient weighing <100 kg. Two 2 mL vials are used when treating patients weighing <100 kg with 4 mg/kg. A 5 mL vial is used when treating patients who weigh >100 kg with a dose of 4 mg/kg. During the period from August 2008 to August 2009, 10 patients received sugammadex 200 mg and 10 received sugammadex 500 mg. The numbers of patients receiving 200 mg or 500 mg of sugammadex between August 2009 and August 2010 were 200 and 50, respectively. The NMBA and reversal budget in the former period was €9410 compared with €15942 in the latter period and this increase was due to the use of sugammadex. While this equates to an increased cost of €6532, Prof. Meistelman points out that the practical over cost per patient is only €2.72. He further adds that the cost of many anaesthetic agents have decreased with development of generics and that in his department this factor has offset the increased expenditure on NMBA reversal agents.

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MSD

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