Muscle Relaxation for Rapid Sequence Induction

François Donati, PhD, MD, FRCPC

Introduction

The term "rapid sequence induction" (RSI) usually applies when tracheal intubation must be performed in a patient who is suspected of having a full stomach and who is at risk for pulmonary aspiration of gastric contents. The goal is to secure the airway without producing any regurgitation and vomiting. The procedure involves three objectives: 1) preventing hypoxia during the induction-intubation sequence; 2) minimizing the time between induction and tracheal intubation, when the airway is unprotected by the patient's reflexes or by the cuffed tracheal tube; and 3) applying measures to decrease the chances of pulmonary aspiration of gastric contents. The first of these objectives is normally met by preoxygenation. Typically, breathing 100% oxygen for 3–5 min before induction of anesthesia allows the patient to sustain apnea for a period of 5–8 min without hypoxia (1). The second objective involves minimization of the induction-intubation interval, which means that a short-acting hypnotic agent should be administered with a neuromuscular blocking agent with a rapid onset of action. Finally, the chance of aspiration is diminished by applying cricoid pressure, by refraining from positive pressure ventilation before tracheal intubation is accomplished, and by waiting until neuromuscular blockade is complete to perform tracheal intubation (Table 1).

All these steps have their detractors. Preoxygenation has been associated with atelectasis (1), but this is a minor problem compared with the added protection afforded by an increase in oxygen contents in the lungs. Application of cricoid pressure has been criticized (2), and positive pressure ventilation has been advocated by some. The role of alternate airway devices, such as the ProSeal laryngeal mask airway (Laryngeal Mask Company Ltd., Jersey, UK) in patients with a full stomach is debated by some. In addition, there is uncertainty regarding which patients should be considered as having a full stomach and who should undergo RSI. The effectiveness of the whole procedure in preventing aspiration of gastric contents has not been evaluated. However, the approach is logical and widely applied.

Emergency cases and poor muscle relaxation at the time of intubation have been identified as predisposing factors for pulmonary aspiration. The purpose of this review is not to consider the indications or the effectiveness of RSI. It will not deal with the different methods of preoxygenation or the controversy about cricoid pressure. In this review, it is assumed that the anesthesiologist has decided that RSI with tracheal intubation is indicated. The most appropriate method to achieve the best possible intubating conditions is discussed, with special emphasis on neuromuscular blocking agents. The judicious use of hypnotic drugs and opioids will also be considered.

History

Concern about aspiration of gastric contents was first raised in 1946 in the obstetric literature, when Mendelson reported 66 cases of aspiration pneumonitis in 44,016 deliveries (15 per 10,000) (3). At that time, women in labor were allowed to eat and drink, and general anesthesia was frequently applied by facemask. Mendelson's article supported the view that patients should fast before anesthesia and surgery but did not resolve the question of induction of anesthesia in a patient with a full stomach for emergency surgery. In 1956, Edwards et al. (4) discussed 1000 perioperative mortality cases in Britain. Of the 589 judged to result from anesthesia, 110 involved regurgitation and vomiting (19%). Efforts were aimed at reducing stomach contents, but aspiration with a stomach tube was found to be both unpleasant and ineffective. In the 1950s, induction with the patient's head up was proposed (5). In 1961, Sellick (6) published his classic paper on cricoid pressure, and the technique was quickly adopted. By the early 1960s, the rules of the game were stated clearly: ". . .the aim is to achieve the placement of an endotracheal tube as rapidly as possible without vomiting and regurgitation. . ." (7), but the methods to achieve this goal were less clear. Some advocated an inhalation induction; an IV induction with thiopental and succinylcholine was only one option. The choice of dose was considered a problem, but recommendations were fuzzy. A review published in

Table 1. Suggested Steps for Rapid Sequence Induction (RSI)

Time (min)	Action
−3 min to 0	Preoxygenation
−3 min (optional)	Precurarization (0.03 mg/kg rocuronium or equivalent)
−1 min (optional)	Small dose opioid
0 min	Induction agent
At loss of consciousness	Cricoid pressure
	Neuromuscular blocking agent: succinylcholine, 1 mg/kg, if no precurarization, or succinylcholine, 2 mg/kg, if precurarization, or rocuronium, 1 mg/kg
	No manual ventilation
+1 to 1.5 min (When blockade complete)	Laryngoscopy and intubation
After intubation	Release of cricoid pressure

1963 noted that "sleep is induced with IV thiopentone as rapidly as possible without depressing respiration. Suxamethonium 50 mg is given IV as soon as sleep occurs" (7). In another 1963 article, it is mentioned that "the choice of drugs and posture is more problematical [than the technique itself]" (8).

In the 1970s, there were occasional reports specifying drug doses in patients requiring RSI. Barr and Thornley (9) published a series of 100 patients who received 50–100 mg succinylcholine. There was "difficulty with intubation" in 7% but no regurgitation or vomiting. Cromartie (10) described rapid sequence induction or "crash induction" in war casualties. The procedure, with preoxygenation, cricoid pressure, and no positive pressure ventilation, is well described. He used precurarization with d-tubocurarine 3 mg and succinylcholine 60–80 mg. A few years later, White (11) administered different induction agents to patients scheduled for emergency surgery, with d-tubocurarine 3 mg before induction and succinylcholine 1.5 mg/kg after induction. The use of a defasciculating agent was obviously the result of a better understanding of succinylcholine pharmacology, which came about after advances in monitoring. No narcotics were administered in any of these studies.

Current Problems and Controversies

Between 1982 and September 2005, there has not been a single study in which RSI was applied to patients scheduled for emergency surgery. All studies dealing with the problem of neuromuscular blockade and intubating conditions during the course of a RSI have used elective patients in whom RSI was simulated. Most of these studies have focused on neuromuscular profile and intubating conditions comparing succinylcholine and nondepolarizing agents. After the demise of rapacuronium, the most interesting of the nondepolarizing agents remains rocuronium, introduced in the 1990s. Still, the dose required to match the intubating qualities of succinylcholine appears to be 1.0 mg/kg, at least in elective patients (12), and that dose of rocuronium is associated with a long duration of action.

The introduction of propofol and remifentanil into clinical practice had the theoretical advantage of modifying the practice of RSI because of the ability of these drugs to improve intubating conditions. Unfortunately, most of the evidence comes from elective patients rather than emergency surgery patients. The difference might not be trivial. Early pharmacokinetics are modified by cardiac output, and the study of this phenomenon has been termed "front-end pharmacokinetics" (13). If cardiac output is decreased, as may happen in emergency patients, the early plasma concentration of a drug is increased because the dose is diluted in a smaller volume.

The question of dose was fuelled by another controversy. A major concern with RSI is what to do if intubation is not possible. The margin of safety is increased if the neuromuscular blocking agent has a duration of action that is shorter than the duration of apnea after proper preoxygenation. Although it was widely believed that such protection could be afforded by succinylcholine 1 mg/kg, recent evidence suggests that this might not be true, and some authors recommend a dose reduction (14). In children, the use of succinylcholine has been questioned because of cases of hyperkalemia and cardiac arrest that are frequently resistant to resuscitative efforts (15). Finally, RSI has been used outside the operating room. Not surprisingly, most studies in the emergency literature suggest that success at intubation is greater if neuromuscular blocking agents are used (16). This means that recommendations have to be formulated for their optimal use.

Physiology and Pharmacology

The patient presumed to have a full stomach and requiring emergency surgery often has physiological alterations that are likely to modify the effect of all IV

Table 2. Influence of Cardiac Output on Onset of Rocuronium[a]

	Ephedrine, 70 μg/kg	Placebo	Esmolol, 0.5 mg/kg
Cardiac output (L/min)	9.1 ± 1.5	8 ± 2.3	5.5 ± 1.2
Rocuronium, 0.6 mg/kg, onset time (s)	52 ± 17	87 ± 7	114 ± 11

[a] After Ezri et al. (19).

drugs, including neuromuscular blocking agents. Hypovolemia might be present and cardiac output may be diminished. In other circumstances, such as fever, sepsis, or hyperdynamic states, cardiac output might actually be increased. Induction of anesthesia produces changes of its own, usually by depressing cardiac output and peripheral vascular resistance.

Rapid onset of action of neuromuscular blocking agents depends on administration of an appropriate dose, leading to a sufficient plasma concentration and rapid delivery to target organs, that is, the neuromuscular junctions of all muscles in the body. However, some muscles are more important than others in the production of adequate intubating conditions. Relaxation of the muscles of the tongue, jaw, vocal cords, diaphragm, and abdominal muscles is more important than relaxation of peripheral muscles. The distinction is not trivial; blood flow and sensitivity to neuromuscular blocking agents vary depending on the location and function of the muscle.

Changes in cardiac output modify the maximum effect of a given dose of a neuromuscular blocking agent and the onset time. When cardiac output decreases, peak plasma concentrations are increased because the drug is diluted in a smaller volume (17). However, the dose normally chosen for intubation produces 100% blockade, so a decrease in cardiac output is likely to still produce 100% blockade. However, a decrease in cardiac output is associated with a longer onset time (17). Also, onset time was found to be increased in elective patients receiving esmolol and decreased in those administered ephedrine (18,19) (Table 2). Intubating conditions were found to be better at 1 min if patients were pretreated with ephedrine (20). It is not indicated to give ephedrine systematically because the drug might produce tachycardia and hypertension. However, these studies demonstrate that if a paralyzing dose of neuromuscular blocking agent is given, time to optimal intubating conditions may be delayed in patients with depressed cardiac output.

Do We Need Neuromuscular Blocking Agents?

With the introduction of propofol as a hypnotic agent and the rapidly acting opioid drugs alfentanil and remifentanil, the need for neuromuscular blocking agents for intubation has been questioned. However, the quality of intubating conditions is less predictable and tracheal intubation becomes frequently impossible if neuromuscular blocking agents are omitted. In elective patients, heavy doses of alfentanil (60 μg/kg) or remifentanil (4 μg/kg) are required to produce conditions that approach those produced by succinylcholine (21). These doses are associated with hypotension, and logic dictates that the occurrence of such hypotensive episodes is likely to be greater in emergency patients. Intubation was impossible in 20% of patients who received alfentanil, 30 μg/kg or less, or remifentanil, 3 μg/kg or less (21) (Table 3).

The need for neuromuscular blocking agents seems obvious when one considers the results obtained by emergency physicians. A review of four studies indicated that failure to intubate occurred in 0%–1.3% in patients in whom RSI with muscle paralysis was applied compared with 8.6%–28% when intubation was performed under sedation only (16). Three attempts were required in 2%–3% of paralyzed patients compared with a 10.7%–24% incidence with sedation only.

Intense neuromuscular blockade can increase the chance of success at tracheal intubation, but it can also benefit the patient. Aspiration is less likely with profound neuromuscular blockade (22). Also, the incidence of laryngeal injuries is less if intubating conditions are excellent, and this situation is more frequent if neuromuscular blocking agents are used (23).

Succinylcholine: Advantages and Pitfalls with a Full Stomach

When the objective is to reduce the induction to intubation interval as much as possible, the advantage of a short-onset drug like succinylcholine is obvious. Succinylcholine has many contraindications, but an additional concern in the RSI context is the increase in intragastric pressure produced by fasciculations. Succinylcholine does increase intragastric pressure but also increases lower esophageal tone, which means that the barrier pressure (intragastric pressure minus lower esophageal tone) remains relatively constant. These changes are small compared with the very large intragastric pressure increases that could be produced as a result of straining and coughing after attempts at intubation in inadequately paralyzed patients.

Table 3. Intubating Conditions Across Studies

Study	Opioid[a]	Induction agent[b]	Neuromuscular blocking agent[b]	Impossible (%)	Poor (%)	Good (%)	Excellent (%)
Kopman et al. (36)	Alfentanil, 12.5	Propofol, 2	None	20	50	20	10
Klemola et al. (21)	Alfentanil, 30	Propofol, 2.5	None	20	10	50	20
Klemola et al. (21)	Remifentanil, 3	Propofol, 2.5	None	20	25	25	30
Klemola et al. (21)	Remifentanil, 4	Propofol, 2.5	None	5	15	25	60
Andrews et al. (12)	None	Propofol, 2.5	Rocuronium, 0.6	2	21	37	40
Andrews et al. (12)	None	Propofol, 2.5	Rocuronium, 1	1	6	27	66
Andrews et al. (12)	None	Propofol, 2.5	Succinylcholine, 1	1	2	23	74
Naguib et al. (14)	Fentanyl, 2	Propofol, 2	Succinylcholine, 1	0	2	18	80
Naguib et al. (14)	Fentanyl, 2	Propofol, 2	Succinylcholine, 0.5	0	6	38	56

[a] Doses in μg/kg.
[b] Doses in mg/kg.

Table 4. Duration of Apnea and Incidence of Desaturation with Succinylcholine

Study	Number of subjects	Succinylcholine dose (mg/kg)	Duration of apnea; min (range)	Incidence of desaturation (%)
Heier et al. (24)	12	1	5.2 (3.5–9.0)	25
Hayes et al. (25)	100	1	4.7	11
Naguib et al. (26)	20	1	4.7 (2–7)	85
Naguib et al. (26)	20	0.56	4.7 (2–12)	65

The rapid onset of action of succinylcholine is a definite advantage for RSI, but a short duration of action is also of great value because the duration of apnea might be shorter than the time to onset of hypoxia. A normal, non-obese, properly preoxygenated adult may sustain 7–8 min of apnea without becoming hypoxic (1). The duration of action of succinylcholine 1 mg/kg at the adductor pollicis is slightly longer, 8–12 min, but the diaphragm recovers before peripheral muscle. At least three studies have tried to tackle this problem. In a small number of volunteers, Heier et al. (24) found that 25% of subjects had a saturation below 80% after a thiopental-succinylcholine sequence, whereas the others started breathing before onset of desaturation. Hayes et al. (25), in a larger number of patients, reported an 11% incidence of hypoxia. Naguib et al. (26), with the same succinylcholine dose, mentioned that 85% of his patients had hypoxia before they started breathing again. In this last study, patients who underwent the same fentanyl-propofol induction sequence, but without succinylcholine, had a 45% incidence of hypoxia (26). Interestingly, the time to resumption of diaphragmatic movements was the same in all three studies cited, 4–5 min (Table 4). There was a greater incidence of desaturation in subjects with larger body mass index (BMI).

What can we conclude from these apparently discordant studies? First, succinylcholine 1 mg/kg does not provide protection against hypoxia in all patients, even if we restrict the discussion to subjects with normal plasma cholinesterase. In all three studies, mean duration of apnea was 4–5 min, but it could be as long as 9 min (Table 4). Second, variability in the effectiveness of preoxygenation may be more important than variability of succinylcholine effect itself. For example, the quantity of oxygen that can be stored is reduced in obese subjects. In the emergency situation, increased oxygen consumption, as may occur in trauma and sepsis, is likely to reduce the safe period. Third, even omitting succinylcholine is not a guarantee that patients will remain normoxic.

Succinylcholine: The Right Dose

The obvious answer to the potential dangers of succinylcholine is to investigate the possibility of reducing the dose. Most studies recognize that a 1 mg/kg dose as the "gold standard," but, until recently, there have been no studies on the relationship between succinylcholine dose and intubating conditions. Examination of large studies in elective patients suggests that 1 mg/kg does not guarantee perfection if intubation is attempted at 1 min (27). Excellent conditions are found in 63%–80% of patients, whereas acceptable (which may involve some diaphragmatic or limb movement) conditions occur in 92%–98% of cases; the remainder are classified as poor or impossible (Table 3). The question was whether the dose could be reduced, in

an attempt to shorten the apnea time, without affecting intubating conditions.

In a study where doses ranging from 0 to 1.0 mg/kg were given, intubating conditions were found to be related to dose, and the dose corresponding to 95% acceptable intubating conditions was determined to be 0.56 mg/kg. Duration at the adductor pollicis of a 0.6 mg/kg dose was found to be 1.5 min shorter than 1 mg/kg, but duration until diaphragmatic movements started again were the same with 0.56 and 1.0 mg/kg (26) (Table 4). This again is probably a reflection of succinylcholine variability. From these studies, it has been recommended to reduce the dose of succinylcholine from 1.0 to 0.6 mg/kg. However, reducing the dose of succinylcholine reduces the incidence of excellent conditions, without a marked decrease in time to return of spontaneous diaphragmatic movements.

Should Precurarization Be Used?

A small dose of non-depolarizing agent given 3–5 min before succinylcholine decreases or eliminates many of the side effects of succinylcholine, such as fasciculations and myalgia (28). Other benefits are reduction of intragastric pressure increases, carbon dioxide production, and incidence of arrhythmia. It is uncertain whether the decrease in oxygen consumption can lead to a significant increase in the possible duration of apnea. However, the major risk is neuromuscular weakness and possible aspiration in the awake patient. In elective patients, there has been an unfortunate inflation in precurarization dosage because the traditional d-tubocurarine 3 mg or 0.05 mg/kg has been abandoned. For example, marked symptoms of neuromuscular weakness have been found after rocuronium 0.06 mg/kg (29). In fact, d-tubocurarine 0.05 mg/kg is equipotent with rocuronium 0.03 mg/kg, both doses being equivalent to 1/10 of the dose producing 95% block (ED_{95}). There are no studies suggesting that this dose is safe or unsafe in patients scheduled for RSI.

It must be recognized, however, that the dose of succinylcholine must be increased if precurarization is used. Dose-response studies suggest that twice as much succinylcholine must be given if precurarization is used. Previous recommendations suggested a dose of 1.5 mg/kg, but it appears that 2 mg/kg with precurarization provides approximately the same onset time and duration as 1 mg/kg without precurarization (30).

Nondepolarizing Drugs

When an adequate dose is administered and if intubation takes place at the appropriate time, intubating conditions are just as good with nondepolarizing agents as with succinylcholine (31). The problem of finding the right moment for intubation can be solved by monitoring. The corrugator supercilii, which moves the eyebrow in response to facial nerve stimulation, has a response to neuromuscular blocking agents that is similar to that of the vocal cords and the diaphragm. If one waits until there is no response at the eyebrow, it is possible to obtain excellent intubating conditions in 80% of patients. This result is obtained with any neuromuscular blocking agent: vecuronium, atracurium, mivacurium, rocuronium, or succinylcholine. The major difference is the time taken to achieve this. Nondepolarizing drugs, in doses approximating $2 \times ED_{95}$, will produce blockade in approximately 2–3 min, whereas succinylcholine will achieve the same result in 1 min. Furthermore, the variability is greater with nondepolarizing agents. If intubation is attempted at 1 min, a rapid onset nondepolarizing drug is required, and rocuronium has the fastest onset. However, many studies have shown that a dose of 0.6 mg/kg produces poorer intubating conditions than succinylcholine and that the dose has to be increased to 1.0 mg/kg to match the effectiveness of succinylcholine (12) (Table 3). However, although the short duration of action of succinylcholine offers some kind of protection against the inability to intubate and ventilate, this is not the case with nondepolarizing agents.

Choice of Opioid and Hypnotic Agent

Opioid agents improve intubation conditions and hemodynamic stability at intubation. However, purists point out that administration of opioids some time before the induction agent might depress airway reflexes and decrease respiratory drive, thus reducing the effectiveness of preoxygenation, and increasing the risk of aspiration and hypoxia during RSI. A compromise is usually reached by giving small doses of opioid drugs. However, with the availability of fast-acting alfentanil and, especially, remifentanil, administration with the induction agent is possible. The effects of these agents on hemodynamics and intubating conditions have not been studied thoroughly when given together with the induction agent. Of interest, one study showed that remifentanil 2 and 4 μg/kg is associated with longer durations of apnea than succinylcholine (32).

When given without neuromuscular blocking agents, propofol is associated with better intubating conditions than either thiopental or etomidate. With succinylcholine, the difference is less apparent but results of large series suggest that intubating conditions are better if the induction agent is propofol rather than thiopental (27). However, onset of neuromuscular blockade is shorter with etomidate than

with either thiopental or propofol (33). Thus, it appears that is more important to choose a paralyzing dose of neuromuscular blocking agent if etomidate is used.

Special Situations

In children, several cases of hyperkalemic cardiac arrest have been associated with the use of succinylcholine (15). These cases are rare, and almost always associated with the previous administration of halogenated agents. Still, unless airway difficulties are expected, it appears prudent to substitute rocuronium for succinylcholine. Onset and duration of rocuronium in the pediatric population is shorter than in adults.

In obstetrics, a smaller functional residual capacity and an increased metabolic rate compared with nonpregnant adults make the safe duration of apnea shorter. Also, pregnancy is associated with decreased plasma cholinesterase activity, so a reduced succinylcholine dose might be indicated. However, the exact dose is not known, as few studies are conducted in this patient population.

The usual contraindications for succinylcholine (burns, upper motor neuron disease, cord transection, muscle dystrophy, preexisting hyperkalemia, severe trauma) of course apply to the emergency situation. In myasthenia gravis, the exquisite sensitivity to nondepolarizing agents precludes the use of precurarization.

The Future

Two interesting developments might influence the way RSI is approached in the future. A new nondepolarizing neuromuscular blocking agent, called gantacurium (previously GW280430A or AV340A), with rapid onset and duration similar to succinylcholine, might become available (34). We do not know whether duration of apnea will be greater than duration of neuromuscular blockade. The predictability of the drug is not known either. The other development constitutes a totally new approach to neuromuscular blockade. A molecule, called sugammadex (previously known as ORG 25969), has been designed to bind rocuronium selectively. It appears that any depth of rocuronium blockade can be antagonized, provided that the right dose of sugammadex is administered (35). This could provide strong protection against the possibility of failure to intubate and ventilate. Availability of sugammadex could make the use of succinylcholine obsolete.

Conclusion

There is limited evidence on the best drug and dose of neuromuscular blocking agent indicated in RSI. Data have to be extrapolated from simulated RSI in elective patients and studies on patients requiring intubation in the emergency room. The use of neuromuscular blocking agents improves intubating conditions, and probably the risk of aspiration, over any induction technique using only opioids and hypnotic agents. Succinylcholine remains the "gold standard" and should be administered unless there are contraindications to its use. The dose of 1 mg/kg without precurarization or 2 mg/kg with precurarization appears to be optimal, providing adequate intubating conditions without prolonged duration. However, protection against hypoxia cannot be guaranteed. Precurarization should be limited to rocuronium 0.03 mg/kg or equivalent. The optimal intubating dose of rocuronium is 1 mg/kg.

References

1. Edmark L, Kostova-Aherdan K, Enlund M, Hedenstierna G. Optimal oxygen concentration during induction of general anesthesia. Anesthesiology 2003;98:28–33.
2. Brimacombe JR, Berry AM. Cricoid pressure. Can J Anaesth 1997;44:414–25.
3. Mendelson CL. The aspiration of stomach contents into the lungs during obstetric anesthesia. Am J Obstet Gynecol 1946;52: 191–205.
4. Edwards G, Morton HJ, Pask EA, Wylie WD. Deaths associated with anaesthesia; a report on 1,000 cases. Anaesthesia 1956;11: 194–220.
5. Snow RG, Nunn JF. Induction of anaesthesia in the foot-down position for patients with a full stomach. Br J Anaesth 1959;31: 493–7.
6. Sellick BA. Cricoid pressure to control regurgitation of stomach contents during induction of anaesthesia. Lancet 1961;2:404–6.
7. Inkster JS. The induction of anaesthesia in patients likely to vomit with special reference to intestinal obstruction. Br J Anaesth 1963;35:160–7.
8. Wylie WD. The use of muscle relaxants at the induction of anaesthesia of patients with a full stomach. Br J Anaesth 1963; 35:168–73.
9. Barr AM, Thornley BA. Thiopentone and suxamethonium crash induction: an assessment of the potential hazards. Anaesthesia 1976;31:23–9.
10. Cromartie RS, III. Rapid anesthesia induction in combat casualties with full stomachs. Anesth Analg 1976;55:74–6.
11. White PF. Comparative evaluation of intravenous agents for rapid sequence induction: thiopental, ketamine, and midazolam. Anesthesiology 1982;57:279–84.
12. Andrews JI, Kumar N, van den Brom RH, et al. A large simple randomized trial of rocuronium versus succinylcholine in rapid-sequence induction of anaesthesia along with propofol. Acta Anaesthesiol Scand 1999;43:4–8.
13. Krejcie TC, Avram MJ. What determines anesthetic induction dose? It's the front-end kinetics, doctor! Anesth Analg 1999;89: 541–4.
14. Naguib M, Samarkandi A, Riad W, Alharby SW. Optimal dose of succinylcholine revisited. Anesthesiology 2003;99:1045–9.

15. Gronert GA. Cardiac arrest after succinylcholine: mortality greater with rhabdomyolysis than receptor upregulation. Anesthesiology 2001;94:523–9.
16. Kovacs G, Law JA, Ross J, et al. Acute airway management in the emergency department by non-anesthesiologists. Can J Anaesth 2004;51:174–80.
17. Kuipers JA, Boer F, Olofsen E, et al. Recirculatory pharmacokinetics and pharmacodynamics of rocuronium in patients: the influence of cardiac output. Anesthesiology 2001;94:47–55.
18. Szmuk P, Ezri T, Chelly JE, Katz J. The onset time of rocuronium is slowed by esmolol and accelerated by ephedrine. Anesth Analg 2000;90:1217–9.
19. Ezri T, Szmuk P, Warters RD, et al. Changes in onset time of rocuronium in patients pretreated with ephedrine and esmolol: the role of cardiac output. Acta Anaesthesiol Scand 2003;47: 1067–72.
20. Tan CH, Onisong MK, Chiu WK. The influence of induction technique on intubating conditions 1 min after rocuronium administration: a comparison of a propofol-ephedrine combination and propofol. Anaesthesia 2002;57:223–6.
21. Klemola UM, Mennander S, Saarnivaara L. Tracheal intubation without the use of muscle relaxants: remifentanil or alfentanil in combination with propofol. Acta Anaesthesiol Scand 2000;44: 465–9.
22. Warner MA, Warner ME, Weber JG. Clinical significance of pulmonary aspiration during the perioperative period. Anesthesiology 1993;78:56–62.
23. Mencke T, Echternach M, Kleinschmidt S, et al. Laryngeal morbidity and quality of tracheal intubation: a randomized controlled trial. Anesthesiology 2003;98:1049–56.
24. Heier T, Feiner JR, Lin J, et al. Hemoglobin desaturation after succinylcholine-induced apnea: a study of the recovery of spontaneous ventilation in healthy volunteers. Anesthesiology 2001; 94:754–9.
25. Hayes AH, Breslin DS, Mirakhur RK, et al. Frequency of haemoglobin desaturation with the use of succinylcholine during rapid sequence induction of anaesthesia. Acta Anaesthesiol Scand 2001;45:746–9.
26. Naguib M, Samarkandi AH, Abdullah K, et al. Succinylcholine dosage and apnea-induced hemoglobin desaturation in patients. Anesthesiology 2005;102:35–40.
27. Donati F. The right dose of succinylcholine. Anesthesiology 2003;99:1037–8.
28. Schreiber JU, Lysakowski C, Fuchs-Buder T, Tramer MR. Prevention of succinylcholine-induced fasciculation and myalgia: a meta-analysis of randomized trials. Anesthesiology 2005;103: 877–84.
29. Mencke T, Schreiber JU, Becker C, et al. Pretreatment before succinylcholine for outpatient anesthesia? Anesth Analg 2002; 94:573–6.
30. Motamed C, Choquette R, Donati F. Rocuronium prevents succinylcholine-induced fasciculations. Can J Anaesth 1997;44: 1262–8.
31. Le Corre F, Plaud B, Benhamou E, Debaene B. Visual estimation of onset time at the orbicularis oculi after five muscle relaxants: application to clinical monitoring of tracheal intubation. Anesth Analg 1999;89:1305–10.
32. McNeil IA, Culbert B, Russell I. Comparison of intubating conditions following propofol and succinylcholine with propofol and remifentanil 2 micrograms kg-1 or 4 micrograms kg-1. Br J Anaesth 2000;85:623–5.
33. Gill RS, Scott RP. Etomidate shortens the onset time of neuromuscular block. Br J Anaesth 1992;69:444–6.
34. Belmont MR, Lien CA, Tjan J, et al. Clinical pharmacology of GW280430A in humans. Anesthesiology 2004;100:768–73.
35. Gijsenbergh F, Ramael S, Houwing N, van Iersel T. First human exposure of Org 25969, a novel agent to reverse the action of rocuronium bromide. Anesthesiology 2005;103:695–703.