Priming with nondepolarizing relaxants for rapid tracheal intubation: a double-blind evaluation

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Results of a series of controlled, randomized, double-blind trials investigating intubation conditions with priming sequences of nondepolarizing relaxants are reported. In Phase I of the study the groups received: Group A, tubocurarine (DTC) 3 mg + succinylcholine 1.5 mg·kg^{-1}, Group B, atracurium 0.05 mg·kg^{-1} + 0.35 mg·kg^{-1}, Group C, vecuronium, 0.01 mg·kg^{-1} + 0.07 mg·kg^{-1}; in Phase II: Group D, no relaxant, Group E, DTC 0.05 mg·kg^{-1} + vecuronium 0.07 mg·kg^{-1}, Group F, vecuronium 0.01 mg·kg^{-1} + vecuronium 0.12 mg·kg^{-1}; in Phase III, Group G, DTC 3 mg + succinylcholine 1.5 mg·kg^{-1}, Group H, vecuronium 0.01 mg·kg^{-1} + 0.09 mg·kg^{-1}, Group I vecuronium 0.1 mg·kg^{-1} as a single bolus. Intubation conditions were assessed at 60 seconds. A seven-minute priming interval was used in Phase I and II and a four-minute interval was used in Phase III. Priming produced significantly better intubating conditions than an equivalent single bolus; however, intubating conditions with priming did not appear to match the uniformly excellent conditions produced by succinylcholine. The data suggest that a four-minute priming interval is as effective as a seven-minute interval. The results of this study differed substantially from previous unblinded studies; therefore, it is suggested that a randomized, double-blind design with simultaneous succinylcholine controls be considered a prerequisite for future studies of intubation conditions.

Key words

NEUROMUSCULAR RELAXANTS: tubocurarine, atracurium, vecuronium, succinylcholine; PHARMACOKINETICS: priming dose; INTUBATION: tracheal.

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Succinylcholine has long been the standard muscle relaxant for facilitation of rapid tracheal intubation. In the patient at high risk for aspiration a rapid-sequence induction with succinylcholine is often utilized. Due to its rapid onset succinylcholine has also retained its position in elective anaesthetic induction. However, succinylcholine has a number of undesirable side-effects, detracting from its use in many clinical settings. Therefore, an alternative relaxant fascilitating intubation as rapidly as succinylcholine would be desirable. It has been suggested that utilizing a divided-dosage regimen, the priming principle, excellent intubating conditions can be rapidly produced with nondepolarizing relaxants alone, thus eliminating the need for succinylcholine.[1,2] This paper reports the results of a series of randomized, double-blind trials investigating this hypothesis.

Methods

This study was conducted in three phases. The first two phases were conducted at Brooke Army Medical Center (BAMC) and the third phase at Landstuhl Army Regional Medical Center (LARMC). The study was approved by the Institutional Review Board at BAMC and by the Hospital Ethics Committee at LARMC. All patients gave written informed consent. Adult ASA physical status I and II patients weighing more than 45 kg and scheduled for elective surgery were eligible for the study. The following patients were excluded; those with asthma, those at high risk for aspiration (e.g., hiatus hernia, pregnancy, morbid obesity), and those in whom a difficult intubation was anticipated. Additionally, any patient with a history of sensitivity to any of the medications specified by the protocol or in whom any of the medications were contraindicated was excluded.

The protocols and dosages are summarized in Figures 1–3. Patients were premedicated with diazepam (10–20 mg PO) adminstered 30–60 minutes before induction. Immediately before the study, medications were prepared in numbered syringes from instructions drawn from a set of randomized envelopes. The investigator preparing the

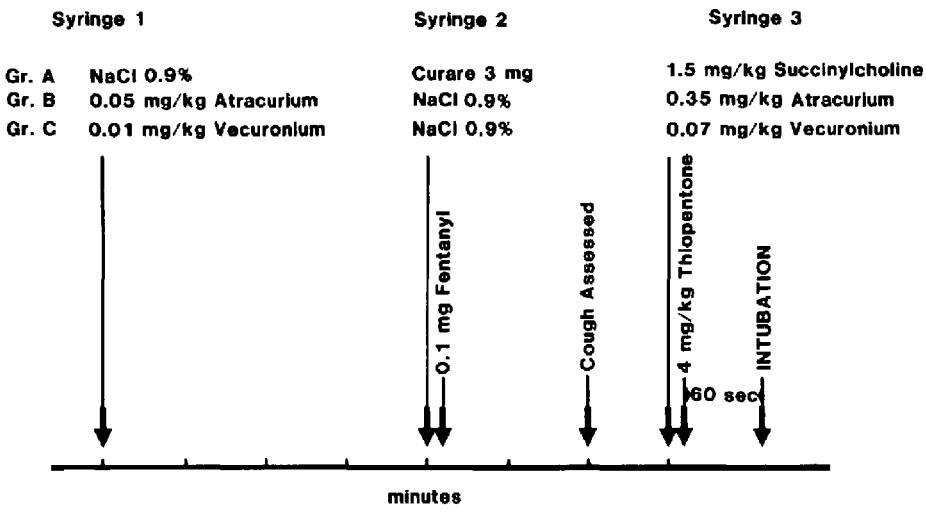

FIGURE 1 Schematic representation of Phase I. Atracurium priming sequence, vecuronium priming sequence and succinylcholine control group.

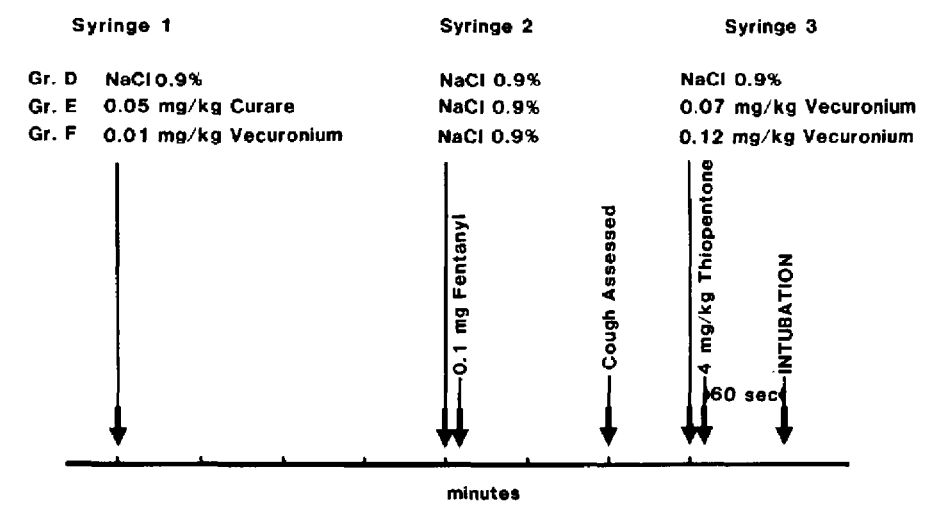

FIGURE 2 Schematic representation of Phase II. Curare-vecuronium priming sequence, vecuronium priming sequence with larger intubating dose and control group given no relaxant.

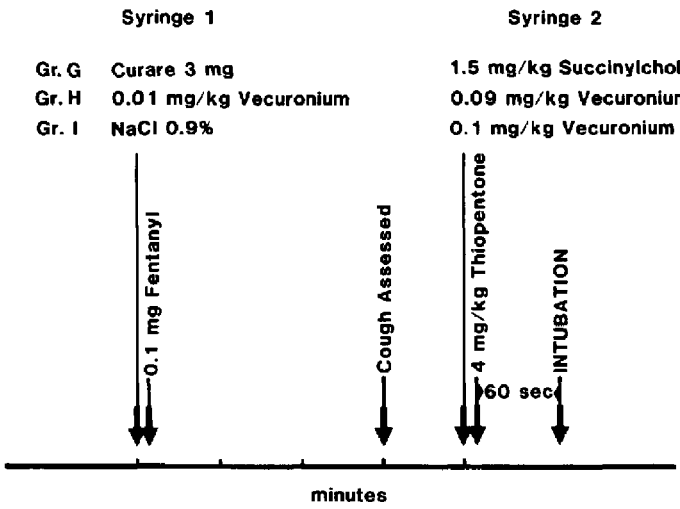

FIGURE 3 Schematic representation of Phase III. Vecuronium priming sequence (four-minute priming interval), control group given no prime, and succinylcholine control group.

syringes was not involved with the induction. Fentanyl and thiopentone were administered from labeled syringes.

All intubations were performed by anaesthetists with at least 18 months' experience. Since LARMC is not a training centre the laryngoscopists in phase III were fully trained anaesthetists or CRNA's. One of the investigators was present for all inductions and recorded the data. The intubation was scored as shown in Table I. One minute prior to administration of the last numbered syringe the patient was asked to cough and the cough was graded as vigorous, weak or absent. Patients were preoxygenated by mask during the induction sequence. After being asked to cough, patients were encouraged to take three to four deep breaths of oxygen. After loss of consciousness, one to two positive pressure breaths were administered by mask. If a patient complained of weakness and was uncomfortable, he/she was asked to cough, the cough was graded, and the induction accelerated by giving the last syringes followed by intubation one minute later.

Several measures were taken to preserve observer blindness. Equivalent syringes were filled to equal volumes with saline (e.g., syringe 1 always contained 3 ml of liquid). As a precaution against interchange of the numbered syringes different sizes were used; for example, in phase I syringe 1 was 3 ml, syringe 2 was 5 ml, and syringe 3 was 10 ml. Since observation of fasciculation would unblind the observers, a defasciculating dose of curare was specified in the succinylcholine groups. A nerve stimulator was not used during the induction since this would unblind the observers. After the data were recorded, the anaesthetist was informed which relaxant had been given so that he/she could plan the remainder of the anaesthetic. The anaesthetists used nerve stimulators during the remainder of the case.

Phase I (Figure 1) was designed to determine if intubating conditions with priming sequences were equivalent to succinlycholine for rapid tracheal intubation. A pilot phase was performed using the dosages advocated by Foldes.[3] These priming dosages (atracurium 0.1 $mg \cdot kg^{-1}$ and vecuronium 0.02 $mg \cdot kg^{-1}$) were double those shown in Figure 1. During the pilot phase these priming doses produced unacceptable side-effects in our lightly premedicated patients. In 3/6 patients receiving these large priming doses the investigators were compelled to ab-

TABLE 1 Grading of intubation conditions

Grade	*Definition*
1	Excellent (easy passage of tube without coughing)
2	Good (passage of tube with slight coughing or bucking, or both)
3	Poor (passage of tube with moderate cough or bucking, or both)
4	Not possible

TABLE II Intubation scores

	Phase I			*Phase II*		
	Group A	*Group B*	*Group C*	*Group D*	*Group E*	*Group F*
Prime dose*	(3 mg dtc)	0.05 mg·kg^{-1} atr	0.01 mg·kg^{-1} vec	NaCl	0.05 mg·kg^{-1} dtc	0.01 mg·kg^{-1} vec
Intub dose	1.5 mg·kg^{-1} suc	0.35 mg·kg^{-1} atr	0.07 mg·kg^{-1} vec	NaCl	0.07 mg·kg^{-1} vec	0.12 mg·kg^{-1} vec
Priming interval	—	7 min	7 min	—	7 min	7 min
Intubation score						
1	15	8	10	0	10	12
2	0	6	5	0	3	3
3	0	1	0	2	2	0
4	0	0	0	2	0	0

	Phase III		
	Group G	*Group H*	*Group I*
Prime dose*	(3 mg dtc)	0.01 mg·kg^{-1} vec	NaCL
Intub dose	1.5 mg·kg^{-1} suc	0.09 mg·kg^{-1} vec	0.1 mg·kg^{-1} vec
Priming interval	—	4 min	—
Intubation score			
1	10	14	4
2	0	0	6
3	0	1	5
4	0	0	0

*Precurarization in Group A and Group G.

breviate the induction sequence as specified by the protocol. After ten patients, the pilot phase was terminated. The priming dosages were then halved to atracurium 0.05 mg·kg^{-1} and vecuronium 0.01 mg·kg^{-1}. The patients receiving the large priming doses in the pilot phase were eliminated from further analysis. Since dosages for the control group were unchanged and since the pilot phase was randomized and double-blind, data for the patients who received succinylcholine in the pilot phase were not discarded. Therefore, Group A consists of four patients from the pilot phase and 11 patients randomized with the 30 patients in Groups B and C.

Phase II (Figure 2) examined two additional priming sequences and a control group which received no relaxant. It became rapidly clear that some form of muscle relaxation was required for intubation in this patient population. After four patients Group D was terminated and Phase II continued with only the two priming groups (E and F).

Phase III (Figure 3) was designed to determine if priming was actually improving conditions over a single bolus of nondepolarizing relaxant. A four-minute priming interval was chosen for Phase III since in the interim Taboada *et al.*[4] presented data based on nerve stimulator studies suggesting that a four-minute priming interval was superior to a seven-minute interval. A succinylcholine control group was included in Phase III to help assure consistency with the other phases.

Results were analyzed using Chi square analysis. When necessary, classes were combined to make the smallest expected value at least one. The Yates continuity correction was applied to 2 × 2 tables.[5] The degrees of freedom for the Chi-square will be noted in a subscript in parenthesis: e.g., $\chi^2_{(3)}$ has three degrees of freedom.

Results

Results are summarized in Table II. Succinylcholine gave uniformly excellent intubating conditions in both Phases I and III. In Phase I all patients were intubated successfully in the priming groups (B, C). Intubating conditions did not equal those of succinylcholine (A vs B, $\chi^2_{(1)} = 6.7$, $p = 0.01$, A vs C, $\chi^2_{(1)} = 3.84$, $p = 0.05$). In Phase II group D which received no relaxant had significantly worse intubating conditions than either of the priming groups ($p = 0.01$). As mentioned in the methods section, this group was terminated after four patients. At the time of termination, we utilized Groups B and C from Phase I for

comparison since there were insufficient patients yet completed in groups E and F to yield a significant test. Simultaneous comparison of all four groups with seven-minute priming intervals (B, C, E, F) yields $\chi^2_{(3)} = 2.4$, $p = 0.5$; suggesting that there is no significant difference between these regimens.

In Phase III it was found that priming significantly improves intubating conditions over an equivalent bolus dose of relaxant (H vs I, $\chi^2_{(2)} = 14.2$, $p < 0.005$). Although intubating conditions with the four-minute priming interval (Group H) were quite good, 1/15 or seven per cent of the patients had less than excellent conditions compared with the uniformly excellent conditions (25/25) found with succinylcholine. Comparison of the four-minute priming interval (Group H) with the groups with the seven-minute intervals (B, C, E, F pooled) yields $\chi^2_{(1)} = 3.0$, $p = 0.07$.

As mentioned in the Methods section, side-effects were a significant problem during the pilot phase when large priming doses were used. After halving the priming doses to those shown in Table II, side-effects became much less apparent. Three of 15 patients in Group B and 1/15 patients in Group C reported weakness, requiring acceleration of the induction sequence in one patient in each group. In Phase II (D, E, F) and Phase III (G, H, I) no patients reported weakness or required acceleration of the induction sequence. Cough was graded one minute before induction and was deemed moderate to weak in 2/15 patients in each of Groups B and C, 1/15 in each of Groups E and F, while all coughs in Group H were graded as vigorous.

Discussion

While all patients in our study were successfully intubated with the use of the various priming sequences, the intubating conditions did not match the uniformly excellent conditions produced by succinylcholine. This differs from the studies of Schwarz *et al.*[1] and Tryba *et al.*,[6] both of whom found no difference in intubating conditions between priming sequences and succinylcholine controls. Several methodological differences may explain the discrepancy. Schwarz *et al.* used a rather small dose of succinylcholine, 0.6 $mg \cdot kg^{-1}$ without precurarization, while we utilized 1.5 $mg \cdot kg^{-1}$ with precurarization. Tryba *et al.* used a variable interval between administration of the intubating dose and intubation based on response to a nerve stimulator, while in our study this interval was held constant. Schwartz *et al.* did not use a blinded design nor were the control groups conducted simultaneously with the priming groups. Tryba *et al.* made an attempt to blind the observer, however, since the succinylcholine was given after the thiopentone while in the other groups the intubating dose was given before the thiopentone, it may have been fairly easy for the observer to penetrate the code.

In Phase III we demonstrated that priming significantly improves intubating conditions compared to an equivalant bolus dose of relaxant. This is consistant with the results of Mirakhur *et al.*[7] Our data suggest that a four-minute priming interval is at least as effective (and perhaps superior) to a seven-minute interval. Our conclusion concerning priming intervals must remain qualified since our study was conducted in separately randomized phases. Statistical tests depend upon simultaneous randomization for complete validity and we did not test the priming intervals simultaneously. The results of Taboada *et al.* based on nerve stimulator data indicated that the four-minute interval could be more effective. Mirakhur did test priming intervals simultaneously and found no difference. Therefore, the clinician is probably justified in adopting the four-minute priming interval.

If priming sequences are to be applied clinically in patients having emergency surgery the priming dose should not cause undue discomfort in the awake patient. While total omission of premedication was not attempted our protocol limited premedication to diazepam 10–20 mg PO 30–60 minutes before induction. Mirakhur utilized the same premedication. This contrasts with the heavy premedication used in other studies. Mehta *et al.*[2] used morphine 0.05–0.15 $mg \cdot kg^{-1}$/M and scopolamine 0.003–0.004 $mg \cdot kg^{-1}$. Priming doses of 0.01 $mg \cdot kg^{-1}$ vecuronium, 0.05 $mg \cdot kg^{-1}$ atracurium, and 0.05 $mg \cdot kg^{-1}$ tubocurarine were well accepted in our patients. Larger priming doses, 0.02 $mg \cdot kg^{-1}$ vecuronium and 0.1 $mg \cdot kg^{-1}$ atracurium, were poorly tolerated. This is consistant with the results of others. Mirakhur *et al.* found a higher incidence of subjective weakness than in our study. We administered fentanyl 100 μg IV during the induction sequence while Mirakhur administered no narcotics until after induction. Therefore, it appears that administration of a small dose of rapidly acting narcotic with the priming dose may improve patient acceptance. This question requires further investigation and has considerable clinical relevance. While many clinicians are comfortable administering small doses of fentanyl in some emergency settings, e.g., appendectomy, they are reluctant to administer such medications in other settings such as Caesarean section.

To be clinically applicable in emergency situations the patient should not be weakened to the point where he can no longer protect his airway. We assessed cough strength to attempt to gauge this consideration. While this was a relatively crude measure and not altogether satisfactory, it was our impression that the patients who received the smaller priming doses retained adequate strength to protect the airway. This is in contrast to the patients in the

pilot phase who received the larger priming doses recommended in the literature, where in 3/6 patients we would have been very concerned had the patient been at high risk. It should be noted that the priming doses used in this study are very similar to the doses recommended for precurization; therefore, the clinician can utilize his experience with precurization when anticipating the effects of the priming dose. It should be noted that as a per cent of the ED_{95} recommended precurization dosages are lower for relaxants such as tubocurarine, for example for a 70 kg man 3 mg is nine per cent of the ED_{95} while 1 mg of pancuronium is 25 per cent of the ED_{95}. This was the rationale for our dosage choice in Group E. We were also exploring the possibility that since tubocurarine has a different spectrum of pre- and post-junctional effects, it might prove to be a superior prime in conjunction with vecuronium. However, our results indicated that this combination did not warrant further investigation.

We have previously discussed the implications of the first phases of our study to the open eye-full stomach patient.[9] The results of the completed study have not changed these implications. Priming sequences do not appear to guarantee excellent intubating conditions. In those patients who "buck" on intubation intraocular pressure may rise more than it would have due to use of succinylcholine. Following the onset of the nondepolarizing relaxant with a peripheral nerve stimulator cannot assure a quiet intubation since onset in peripheral muscles may not correlate with onset in the diaphragm.[10,11] A recent case report[12] describes the use of a priming sequence in an intoxicated patient with an open eye injury. The priming dose was 0.02 $mg \cdot kg^{-1}$ vecuronium. The patient became very distressed and may have aspirated during the induction. It appears that the use of succinylcholine with precurization can still be justified and indeed is probably superior to priming in the open eye-full stomach situation.[13–15]

In this study the interval from the conclusion of the injection of the intubating dose and thiopentone (see Figures 1–3) until intubation was 60 seconds. We felt most anaesthetists would feel comfortable with this interval in the emergency setting. Savaresse[16] suggested that an interval of 90 seconds is required for priming sequences. We suggest that many anaesthetists are uncomfortable with a 90-second interval. Since intubating conditions with priming are produced by a combination of anaesthetic depth and neuromuscular blockade, it is possible that the induction agent could redistribute from the brain faster than the neuromuscular blockade solidifies, with intubation conditions worsening with increased time. Further studies are required to assess if a 90-second interval is superior to 60 seconds. As apnoea intervals are lengthened in future studies, it would probably be prudent to monitor the experimental subjects with pulse oximetry.

Priming does not appear to provide a significant advantage over succinylcholine in the emergency setting. However, priming may have a place in routine practice, especially day surgery, when tracheal intubation is planned. Succinylcholine-induced muscle pain may be a significant problem in ambulatory patients[17] so that its avoidance may be desirable. With the seven-minute priming interval initially recommended, it was difficult to contemplate priming in a busy operating list. Since an occasional patient may still become distressed even with the smaller priming doses, we cannot concur with the recommendation of Schwarz *et al.*[1] that the "prime" be administered in the hallway or holding area. However, our study and the study of Mirakhur *et al.* demonstrate that a four-minute interval is at least as effective. This is the same as the time required for an effective defasciculating dose prior to succinylcholine. Mirakhur *et al.* did not find uniformly acceptable (defined as good or excellent) intubating conditions with priming sequences. In contrast, the vecuronium priming groups (C, F, H) in our study provided acceptable conditions in 98 per cent of the patients. This difference is probably explained by the difference in control groups. Mirakhur *et al.* did not include a simultaneous succinylcholine control group. In our study succinylcholine control groups were included in Phase I and III. Kirkpatrick[18] suggested that succinylcholine control groups be included in any study of intubating conditions. Our study confirms this caveat. If further studies confirm that priming produces acceptable conditions in a high percentage of patients, its major role may be elective cases in busy operating lists.

In conclusion, this randomized, double-blind study demonstrated that priming sequences of nondepolarizing relaxants allow rapid tracheal intubation. Priming produces significantly better intubating conditions than can be produced with an equivalant single bolus. However, intubating conditions with priming do not appear to match the uniformly excellent conditions which can be produced with succinylcholine.

The results of this blinded study differed from previous unblinded studies. It appears that a randomized, double-blind design with simultaneous succinylcholine controls is an important prerequisite for studies of intubation conditions.

Acknowledgment

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References

1 *Schwarz S, Ilias W, Lackner F, Mayrhofer O, Foldes FF.* Rapid tracheal intubation with vecuronium: the priming principle. Anesthesiology 1985; 62: 388–91.

2 *Mehta MP, Choi WW, Gerghis SD, Sokoll MD, Adolphson AJ.* Facilitation of rapid endotracheal intubations with divided doses of nondepolarizing neuromuscular blocking drugs. Anesthesiology 1985; 62: 392–5.

3 *Foldes FF.* Rapid tracheal intubation with nondepolarizing neuromuscular blocking drugs: the priming principle. Br J Anaesth 1984; 56: 663.

4 *Taboada JA, Rupp SM, Miller RD.* Refining the priming principle for vecuronium during rapid-sequence induction of anesthesia. Anesthesiology 1986; 64: 243–7.

5 *Snedecor GW, Cochran WG.* Statistical Methods. Ames, Iowa. Iowa State Press, 1967: 199–257.

6 *Tryba M, Zevounou F, Zenz M.* Vecuronium zur blitz-intubation. Anaesthesist 1986; 35: 509–13.

7 *Mirakhur RK, Lavery GG, Gibson FM, Clarke RSJ.* Intubating conditions after vecuronium and atracurium given in divided doses (the priming technique). Acta Anaesthesiol Scand 1986; 30: 347–50.

8 *Engbaek J, Howardy-Hansen P, Ording H, Viby-Mogensen.* Precurarization with vecuronium and pancuronium in awake, healthy volunteers: the influence on neuromuscular transmission and pulmonary function. Acta Anaesthesiol Scand 1985; 29: 117–20.

9 *Baumgarten RK, Reynolds WJ.* The priming principle and the open eye-full stomach. Anesthesiology 1985; 63: 561–2.

10 *Tran DQ, Amaki Y, Ohta Y, Nagashimi H, Duncalf D, Foldes FF.* Simultaneous in vivo measurement of NM block on three muscles (Abstract). Anesthesiology 1982; 57: A276.

11 *Bencini A, Newton DEF.* Rate of onset of good intubating conditions, respiratory depression and hand muscle paralysis after vecuronium. Br J Anaesth 1984; 56: 959–65.

12 *Musich J, Walts LF.* Pulmonary aspiration after a priming dose of vecuronium. Anesthesiology 1986; 64: 517–8.

13 *Libonati MM, Leahy JJ, Ellison N.* The use of succinylcholine in open eye surgery. Anesthesiology 1985; 62: 637–40.

14 *Oppenheimer P.* Open eye-full stomach. *In*: Anesthesia for Ophthalmology. Bruce RA, McGoldrick KE, Oppenheimer P (eds). Birmingham. Aesculapius. 1982; 188–9.

15 *Cunningham AJ, Barry P.* Intraocular pressure – physiology and implications for anaesthetic management. Can Anaesth Soc J 1986; 33: 195–208.

16 *Savarese JJ.* Clinical relaxation: current controversy. Can Anaesth Soc J 1986; 33: S1–S4.

17 *Adams AP.* Comment on "Diazepam does not prevent succinylcholine-induced fasciculations and myalgia." Survey of Anesthesiology 1985; 29: 221–2.

18 *Kirkpatrick AF.* Rapid-sequence induction: vecuronium versus pancuronium versus succinylcholine? (Letter) Anesthesiology 1986; 65: 443–4.

Résumé

Les résultats d'une série d'études contrôlées, randomisées et à double-insu investiguant les conditions d'intubation avec des séquences d'amorce de relaxants musculaires non dépolarisants sont rapportés. Dans la première phase les groupes ont reçu: Groupe A, curare 3 mg + succinylcholine 1.5 mg·kg^{-1}, Groupe B, atracurium 0.05 mg·kg^{-1} + 0.35 mg·kg^{-1} Groupe C, vécuronium 0.01 mg·kg^{-1} + 0.07 mg·kg^{-1}; dans la phase II: Groupe D, aucun relaxant, Groupe E, curare 0.05 mg·kg^{-1} + vécuronium 0.07 mg·kg^{-1}, Groupe F, vécuronium 0.01 mg·kg^{-1} + vécuronium 0.12 mg·kg^{-1}; dans la phase III: Groupe G, curare 3 mg + succinylcholine 1.5 mg·kg^{-1}, Groupe H, vécuronium 0.01 mg·kg^{-1} + 0.09 mg·kg^{-1}, Groupe I, vécuronium 0.1 mg·kg^{-1} en une dose unique. Les conditions d'intubation étaient évaluées aprés 60 secondes. Un interval de sept minutes a été utilisé dans les phases I et II et un interval de quatre minutes fut utilisé pour la phase III. L'amorcage a offert des conditions d'intubation significativement meilleures qu'avec des doses uniques équivalentes. Cependant les conditions d'intubation après amorcage n'étaient pas uniformément excellentes comme les conditions produites par la succinylcholine. Les données suggérent qu'un interval d'amorcage de quatre minutes est aussi efficace qu'un interval de sept minutes. Les résultats de cette étude diffèrent substantiellement des études précédentes qui n'étaient pas à double insu. Ainsi il est suggéré qu'une étude randomisée à double insu avec des groupes contrôle simultanés avec la succinylcholine soient considérés comme un prérequis pour des futures études sur les conditions d'intubation.