Comparison of the effects of succinylcholine and atracurium on intracranial pressure in monkeys with intracranial hypertension

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The effects of succinylcholine (1.5 mg·kg^{-1} IV) administered five minutes after a defasciculating dose of curare (0.05 mg·kg^{-1} IV), were compared with the effects of atracurium (0.5 mg·kg^{-1} IV) on intracranial pressure (ICP) in 13 cynomologus monkeys with intracranial hypertension (ICP ~ 25 mmHg). Neither succinylcholine nor atracurium increased ICP during general anaesthesia with 60 per cent N_2O/O_2, 0.5–1 per cent halothane. During a rapid sequence induction and intubation with thiopentone 5 mg·kg^{-1} IV, ICP increased equally with intubation following both atracurium (25 ± 1 to 32 ± 2 mmHg) and succinylcholine (25 ± 1 to 31 ± 2 mmHg) ($p < 0.05$). Intubation was also associated with significant increases in $PaCO_2$, CVP and MAP. We conclude that in this primate model of intracranial hypertension, neither atracurium nor succinylcholine (when given following a defasciculating dose of curare) elevates ICP. In terms of the elevation of ICP associated with intubation, atracurium was found to offer no advantage over succinylcholine.

Key words
NEUROMUSCULAR RELAXANTS: atracurium, succinylcholine; BRAIN: intracranial pressure, intracranial hypertension.

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Succinylcholine is the muscle relaxant of choice when neuromuscular blockade of rapid onset and short duration is desired.[1,2] However, because succinylcholine has been reported to increase intracranial pressure (ICP),[3–8] previous workers have recommended that for patients with elevated ICP, succinylcholine be avoided in favour of a non-depolarizing muscle relaxant.[3,6–8] However, the clinical recommendations concerning the use of succinylcholine in patients with increased ICP are not based on well controlled experimental studies.

Previous investigations have yielded conflicting results because factors known to affect ICP such as $PaCO_2$[5,7,9,10] central venous pressure (CVP)[3,5–7,9,10] mean arterial pressure (MAP)[5,7] and anaesthesia[7,8] were not controlled or measured. Also, statistical analysis[5–8] and comparison with another muscle relaxant to control for the effects of muscle relaxation and positive pressure ventilation were not performed.[3–5] Furthermore, only one study attempted to prevent fasciculation,[8] which may raise ICP.[6] Also in several studies the majority of the subjects did not have intracranial hypertension.[4,5,9–11]

These uncertainties have resulted in controversy over the administration of succinylcholine in situations where the rapid paralysis achieved with succinylcholine would be desirable, such as the patient with increased intracranial pressure and a full stomach, who requires intubation. Therefore, we reexamined the ICP response to succinylcholine in a primate model with intracranial hypertension to

determine if succinylcholine increased ICP when fasciculation was prevented by a small dose of curare and factors such as $PaCO_2$, CVP, MAP, intubation and positive pressure ventilation were controlled. We examined the response during general anaesthesia in order to obtain stable conditions in terms of the confounding variables mentioned above. We also examined the response during a rapid sequence induction and intubation which mimics both the clinical situation and the conditions of many of the earlier studies which examined the response of ICP to succinylcholine. Atracurium was investigated because its effects on ICP had not been reported and it served as a control for the effects of paralysis and positive pressure ventilation during the rapid sequence induction and intubation.

Methods

Thirteen fasted cynomologus monkeys (5.6–8.1 kg, mean 6.5 kg) were anaesthetized with 60 per cent N_2O/O_2, 0.5–1 per cent halothane, intubated with cuffed endotracheal tubes and mechanically ventilated (Harvard ventilator) without use of muscle relaxants. Arterial CO_2 was maintained between 33–38 mmHg. A femoral artery and vein were cannulated to measure arterial and central venous pressures. Thumb twitch tension in response to 1 Hz supramaximal ulnar nerve stimulation was measured with a force transducer (Grass Instruments Inc.).

Intracranial pressure was measured via a subarachnoid catheter over the parietal cortex which was sealed in place with cyanoacrylate glue. The measurements were accepted if both arterial and ventilatory variations were evident in the ICP tracing. This method of measuring ICP has been shown to correlate with ICP measurements in the cisterna magna over an ICP range of 8–38 mmHg.[11] An epidural catheter was sealed in place in the same manner over the opposite parietal cortex. ICP was slowly increased to 25 mmHg by infusion of ten per cent hydroxyethyl starch (Hetastarch, McGaw Labs) into the epidural space. The ICP was considered stable if it remained at 25 ± 1 mmHg for 15 min without additional infusion of hetastarch.

End tidal CO_2, thumb twitch tension, MAP, CVP, and ICP were continuously recorded on a Grass Polygraph (Model MP-7). All pressure transducers were zeroed to the midaxillary line with the monkey in the supine position (the monkeys were restrained supine in a monkey chair during the study). Temperature was measured with a rectal temperature probe and maintained at 37 ± 0.5°C with a heating blanket and lamps.

Each study was carried out in two parts.

Part I – The monkeys were mechanically ventilated with 60 per cent N_2O/O_2 and halothane 0.5–1.0 per cent. The per cent inspired halothane was adjusted to provide surgical anaesthesia and thereafter was kept constant throughout the study. $PaCO_2$ was held constant and mild hyperventilation (group range $PaCO_2$ 33–38 mmHg) was maintained to prevent interference from spontaneous ventilation. After all monitored variables had stabilized and control values obtained, either atracurium (Tracrium, Burroughs Wellcome Co.) 0.5 $mg \cdot kg^{-1}$ or succinylcholine (Anectine, Burroughs Wellcome Co.) 1.5 $mg \cdot kg^{-1}$ was administered IV. Curare (Tubocurare, Abbott Laboratories) 0.05 $mg \cdot kg^{-1}$ IV was given 5 min prior to succinylcholine.

The first seven monkeys received succinylcholine as the initial muscle relaxant and the last six received atracurium. Arterial blood gas samples were obtained immediately before muscle relaxant administration and shortly after the loss of the twitch response. The pressure data were obtained at control and at the point of maximal change. Twenty minutes after the thumb twitch had returned to the control level, the alternate muscle relaxant was administered and the study repeated.

Part II – At the completion of Part I and 20 minutes after the twitch response had returned to control, the monkeys were extubated and allowed to awaken while supine in the chair. After stable baseline recordings were obtained, anaesthesia was induced with thiopentone 5 $mg \cdot kg^{-1}$ IV followed

TABLE 1 Response of intracranial pressure (ICP) to succinylcholine and atracurium during N_2O/O_2/halothane anaesthesia (mmHg, mean ± SE, n = 13)

Study Period	*MAP*	*CVP*	*$PaCO_2$*	*ICP*
Control	74 ± 2	9 ± 1	33 ± 1	25 ± 1
Succinylcholine* (1.5 $mg \cdot kg^{-1}$)	75 ± 2	9 ± 1	34 ± 1	26 ± 1
Control	76 ± 4	9 ± 1	35 ± 1	25 ± 1
Atracurium (0.5 $mg \cdot kg^{-1}$)	73 ± 4	8 ± 1	36 ± 1	24 ± 1

*Curare 0.05 $mg \cdot kg^{-1}$ IV administered 5 min before succinylcholine.

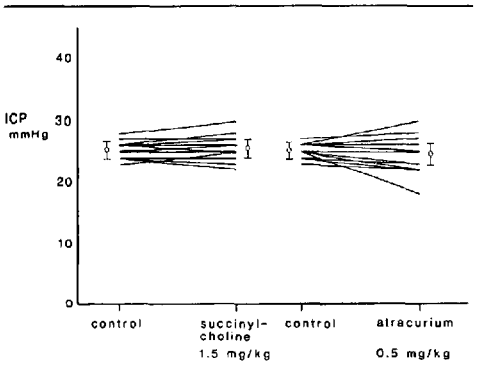

FIGURE 1 Effect of succinylcholine and atracurium on intracranial pressure (ICP) during N_2O/O_2/halothane anaesthesia. Open circles represent mean ± SE.

immediately by either atracurium 0.5 mg·kg^{-1} IV or succinylcholine 1.5 mg·kg^{-1} IV. Curare 0.05 mg·kg^{-1} IV was given five minutes prior to induction to those animals who were to receive succinylcholine. Preoxygenation was performed by directing a flow of oxygen onto the monkey's face. Arterial blood gas samples were withdrawn just before induction and immediately after intubation. Physiologic variables were analyzed at control (just before thiopentone), after muscle relaxant (with loss of the twitch response, i.e., before intubation), and at the peak ICP response following intubation. After intubation the monkeys were maintained on 60 per cent N_2O/O_2/halothane 0.5–1 per cent until the twitch had been at control for 20 minutes. The monkeys were then extubated, allowed to awaken, and the sequence repeated using the alternate muscle relaxant.

Differences between the four data sets (control, succinylcholine, control, atracurium) were detected by application of ANOVA. Individual interset comparisons were then tested for significance using the Student-Newman-Keuls Test with a significance level of $p < 0.05$. All values are given as mean ± SE.

Results

Part I – Effects during 60% N_2O/O_2, 0.5–1.0% halothane anaesthesia

The monitored variables were similar during the two control intervals preceding the injection of succinylcholine and atracurium (Table I). Neither succinylcholine nor atracurium affected ICP (Figure 1). Mean arterial pressure, CVP and $PaCO_2$ were unchanged. Fasciculation did not occur with succinylcholine.

Part II – Effects during rapid sequence induction and intubation

As in part I, the monitored variables in the control intervals before administration of the muscle relaxants were similar (Table II). The slight hyperventilation observed is of the same magnitude as that in Part I and was secondary to anxiety, since the monkeys were not sedated. Following both succinylcholine and atracurium, significant and identical increases in MAP, CVP and $PaCO_2$ occurred in association with intubation. The time from administration of thiopentone until intubation was 55 ± 4 sec after succinylcholine and 50 ± 6 sec after atracurium. Again neither succinylcholine nor atracurium affected ICP (Figure 2). Fasciculation did not occur. Intubation, however, increased ICP from control, but the increase was similar with both muscle relaxants, namely from 25 ± 1 to 32 ± 2 mmHg ($p < 0.05$) following atracurium and from 25 ± 1 to 31 ± 2 mmHg ($p < 0.05$) after succinylcholine.

Discussion

Our study demonstrates that succinylcholine does not increase ICP in monkeys with intracranial hypertension when fasciculation is prevented and variables known to influence ICP such as MAP,

TABLE II Response of intracranial pressure (ICP) to succinylcholine and atracurium during a rapid sequence induction and intubation with thiopentone 5 mg·kg^{-1} IV (mmHg, mean ± SE, n = 13)

Study Period	*MAP*	*CVP*	*$PaCO_2$*	*ICP*
Control	102 ± 5	6 ± 1	33 ± 1	25 ± 1
Succinylcholine‡ (1.5 mg·kg^{-1})	104 ± 6	8 ± 1	—	24 ± 1
Intubation	117 ± 6*	9 ± 1*	38 ± 2*	31 ± 2*
Control	99 ± 6	6 ± 1	34 ± 1	25 ± 1
Atracurium (0.5 mg·kg^{-1})	96 ± 6	8 ± 1	—	26 ± 1
Intubation	109 ± 6†	9 ± 1†	37 ± 1†	32 ± 2†

*$p < 0.05$ compared to control.
†$p < 0.05$ compared to control, not different from intubation following succinylcholine.
‡Curare 0.05 mg·kg^{-1} IV, given 5 min before induction.

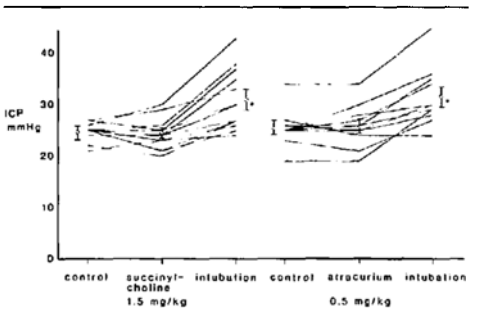

FIGURE 2 Effect of succinylcholine and atracurium on intracranial pressure (ICP) during a rapid sequence induction with thiopentone 5 $mg \cdot kg^{-1}$. Open circles represent mean ± SE. *Significantly different from control $p < 0.05$. Not significantly different from each other.

CVP, $PaCO_2$, and intubation are controlled. Following both succinylcholine and atracurium, ICP increased only with intubation, which was associated with increases in MAP, CVP, and $PaCO_2$. This suggests that apnoea, intubation, and subsequent positive pressure ventilation, rather than the muscle relaxant caused ICP to rise.

Previous studies examining the ICP response to succinylcholine have produced conflicting results. Several investigators have reported increases in ICP with the administration of succinylcholine.[3–7] However, these studies did not use precurarization and did not control for CVP,[5–7] $PaCO_2$,[5,7] MAP,[5,7] or time from barbiturate induction to intubation.[7] They also lack adequate statistical analysis[5–7] and a control muscle relaxant to control for the effects of positive pressure ventilation and intubation.[4,5]

While fasciculation is associated with an elevation of ICP,[6] Cottrell *et al.*[3] recently reported a consistent rise in ICP in cats following succinylcholine which did not always occur with fasciculation. They hypothesized that the increase in ICP might be due to central venoconstriction caused by the adrenergic effects of succinylcholine, but CVP was not reported and pulmonary wedge pressure could be obtained only in one animal. Also, species-specific cardiovascular responses to succinylcholine occur[13] making inferences across species difficult. Succinylcholine did not change CVP or MAP in this study. This may reflect differences resulting from anaesthetic depth or species response.

McLeskey *et al.*[8] did precurarize their patients and also found that succinylcholine did not increase ICP prior to intubation. Following intubation they observed that ICP increased in two of four patients when succinylcholine was the muscle relaxant compared with one of 12 patients paralyzed with pancuronium. They concluded that pancuronium was preferable to succinylcholine in high risk neurosurgical patients. However, statistical analysis of their data demonstrates no significant difference in ICP elevation between the two groups. Our findings are therefore in agreement with their data.

We also demonstrated that atracurium does not increase ICP in primates with intracranial hypertension. Since our study was completed preliminary investigations in cats[14] and humans[15] have reported similar results.

Because we did not find an increase in ICP with succinylcholine, the validity and sensitivity of our model to detect increases in ICP must be discussed. First, the use of a subarachnoid, supracortical catheter to measure ICP has been previously documented as accurately reflecting ICP over a range of 8–38 mmHg when compared to ICP measured by a cisterna magna catheter.[11] Second, our primate model can detect changes in ICP as illustrated by the presence of arterial pulse and ventilation-induced variations in the ICP. Also, increases in ICP were observed with intubation even after a large dose of thiopentone. Third, the experimental model used was biased towards the detection of an increase in ICP because of the intracranial hypertension induced in the control state. Although intracranial compliance was not measured it is known to decrease as ICP rises.[16] Accordingly, we observed that the amplitude of the arterial pulse in the ICP tracing increased as we increased the ICP, indicating a reduction in compliance.[16]

Halothane and N_2O were selected because their effects on cerebral autoregulation and ICP are detrimental rather than protective.[17] While the monkeys were slightly hyperventilated, which should induce cerebral vasoconstriction, this effect would be minimal in the presence of halothane.[17] Furthermore, studies on hyperventilated subjects have reported increases in ICP after succinylcholine.[3–5] Therefore, we believe our ICP measurements are accurate and that if succinylcholine had increased ICP it would have been detected.

In summary, we have shown that in monkeys with intracranial hypertension, succinylcholine

(1.5 $mg \cdot kg^{-1}$ IV), administered five minutes after a defasciculating dose of curare (0.05 $mg \cdot kg^{-1}$), does not raise ICP. Atracurium is also without effect on ICP. Although these results need to be confirmed in humans, they suggest that either muscle relaxant might be used safely in humans with increased ICP. Paralysis, when associated with apnoea, intubation, and positive pressure ventilation, results in increases in MAP, CVP, and $PaCO_2$ which elevates ICP. These factors must be controlled in order to assess effects on ICP attributable to muscle relaxants.

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References

1 *Miller RD, Rupp SM, Fisher DM, Cronnelly R, Fahey MR, Sohn YJ.* Clinical Pharmacology of vecuronium and atracurium. Anesthesiology 1984; 61: 444–53.

2 *Brown EM, Krishnaprasad D, Smiler BG.* Pancuronium for rapid induction technique for tracheal intubation. Can Anaesth Soc J 1979; 26: 489–91.

3 *Cottrell JE, Hartung J, Giffin JP, Shwiry B.* Intracranial and hemodynamic changes after succinylcholine administration in cats. Anesth Analg 1983; 62: 1006–9.

4 *Marsh ML, Dunlop BJ, Shapiro HM, Gagnon RL, Rockoff MA.* Succinylcholine-intracranial pressure effects in neurosurgical patients (Abstract). Anesth Analg 1980; 59: 550–1.

5 *Halldin M, Wåhlin Å.* Effect of succinylcholine on the intraspinal fluid pressure. Acta Anaesthesiol Scand 1959; 3: 155–61.

6 *Søndergård W.* Intracranial pressure during general anaesthesia. Danish Medical Bulletin 1961; 8: 18–25.

7 *Lewelt W, Moszyński K, Koźniewska H.* Effects of depolarizing, non-depolarizing muscle relaxants and intubation on the ventricular fluid pressure. *In:* Beks JWF, Bosch DA, Brock M, eds. Intracranial pressure III. Berlin: Springer-Verlag 1976; 215–8.

8 *McLeskey CH, Cullen BF, Kennedy RD, Galindo A.* Control of cerebral perfusion pressure during induction of anesthesia in high-risk neurosurgical patients. Anesth Analg 1974; 53: 985–92.

9 *Lam AM, Nicholas JF, Manninen PH.* Influence of succinylcholine on lumbar cerebral spinal pressure in man (Abstract). Anesth Analg 1984; 63: 240.

10 *White PF, Schlobohm RM, Pitts LH, Lindauer JM.* A randomized study of drugs for preventing increases in intracranial pressure during endotracheal suctioning. Anesthesiology 1982; 57: 242–4.

11 *Weiss MH, Wertman N, Apuzzo MLJ, Heiden JS, Kurze T.* The influence of myoneural blockers on intracranial dynamics. Bulletin of the Los Angeles Neurological Societies 1977; 42: 1–7.

12 *Snyder JV, Nemoto EM, Carroll RG, Safar P.* Global ischemia in dogs: intracranial pressure, brain blood flow and metabolism. Stroke 1975; 6: 21–7.

13 *Collins CC, Bach-y-Rita P.* Succinylcholine, ocular pressure, and extraocular muscle tension in cats and rabbits. J Appl Physiol 1972; 33: 788–91.

14 *Litwak B, Giffin JP, Cottrell JE, Capuano C, Stein C.* Intracranial pressure after atracurium in cats (Abstract). Anesth Analg 1985; 64: 249.

15 *Minton MD, Stirt JA, Bedford RF.* Atracurium and intracranial pressure in man (Abstract). Anesth Analg 1985; 64: 257.

16 *Avezaat CJJ, Van Eijndhoven JHM, Wyper DJ.* Cerebrospinal fluid pulse pressure and intracranial volume-pressure relationships. Journal of Neurology, Neurosurgery, and Psychiatry 1979; 42: 687–700.

17 *Messick JM Jr, Mewberg LA, Nugent M, Faust RJ.* Principles of neuroanesthesia for the non-neurosurgical patient with CNS pathophysiology. Anesth Analg 1985; 64: 143–74.

Résumé

Les effets de l'administration de succinylcholine (1.5 $mg \cdot kg^{-1}$) cinq minutes après une dose qui empêche la fasciculation de curare (0.05 $mg \cdot kg^{-1}$ IV) ont été comparés avec les effets de l'atracurium (0.5 $mg \cdot kg^{-1}$ IV) sur la pression intracrânienne (ICP) chez 13 singes cynomologus avec hypertension intracrânienne (ICP ~ 25 mmHg). Ni la succinylcholine ni l'atracurium ont augmenté la pression intracrânienne lors de l'anesthésie générale avec 60 pour cent de protoxyde d'azote/oxygène, et 0.5–1 pour cent d'halothane. Lors de l'induction à séquence rapide et l'intubation avec le thiopentone 5 $mg \cdot kg^{-1}$ IV, la pression intracrânienne a augmenté également avec l'intubation suite à l'atracurium (25 ± 1 à 32 ± 2 mmHg) et le succinylcholine

(25 ± 1 à 31 ± 2 mmHg) ($p < 0.05$). L'intubation a aussi été associée avec une augmentation significative de la $PaCO_2$, la pression veineuse centrale et la pression artérielle moyenne. On conclut que pour un seul modèle de primate en hypertension intracrânienne, ni l'atracurium ni la succinylcholine (lorsque donné après une dose de curare empêchant la fasciculation) n'augmentent la pression intracrânienne. Quant à l'augmentation de la pression intracrânienne lors de l'intubation, l'atracurium n'a pas offert davantage sur la succinylcholine.