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Increases in Intracranial Pressure from Succinylcholine: Prevention by Prior Nondepolarizing Blockade

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Whether succinylcholine causes an increase in intracranial pressure (ICP) in patients with brain lesions is uncertain and, if increased ICP does occur, its pathophysiology remains unknown. The authors investigated both the effect of succinylcholine on ICP and its modification with prior neuromuscular blockade by measuring ICP (subarachnoid bolt) in 13 consecutive patients with brain tumors who received succinylcholine both before and after complete neuromuscular blockade with vecuronium. Anesthesia was induced with thiopental, 6 mg · kg^{-1} iv, and nitrous oxide, 70% in oxygen, while ventilation was controlled (Pa_{CO_2} = 37.2 mmHg ± 1.7 SE). Succinylcholine, 1 mg · kg^{-1} iv, was administered and ICP, heart rate (HR), and blood pressure (BP) were recorded until normal twitch tension was restored. Complete neuromuscular blockade was then established with vecuronium, 0.14 mg · kg^{-1} iv; 3 min later, succinylcholine, 1 mg · kg^{-1} iv, was repeated. The resulting changes in ICP, HR, and BP were recorded for 3 min. Following the first dose of succinylcholine, mean ICP increased from 15.2 mmHg ± 1.3 SE to 20.1 mmHg ± 2.0 SE ($P < 0.05$), with five of the patients sustaining increases in ICP of 9 mmHg or greater. In contrast, when succinylcholine was given after vecuronium-induced paralysis, no patient developed an increase in ICP greater than 3 mmHg ($P < 0.05$ compared with the incidence of ICP ≥ 9 mmHg observed after the first dose of succinylcholine). A second group of six patients received two doses of succinylcholine according to the same protocol but without an intervening dose of vecuronium. These patients sustained increased ICP after both doses of succinylcholine. The authors conclude that increases in ICP may be induced by succinylcholine in patients with compromised intracranial compliance and the possibility of such an increase should be considered in their anesthetic management. While the exact mechanism of this phenomenon remains unknown, the results indicate that complete neuromuscular blockade with vecuronium prevents succinylcholine-induced increases in ICP. (Key words: Brain: intracranial pressure. Muscle, skeletal: fasciculation. Neuromuscular relaxants: succinylcholine; vecuronium.)

THE ABILITY OF SUCCINYLCHOLINE (Sch) to produce rapid, profound, yet brief neuromuscular blockade has led to its widespread use in the practice of anesthesia. However, the safety and appropriateness of its use in neurosurgical operations remain controversial. Some clinical and laboratory studies suggest that Sch may cause elevations of intracranial or cerebrospinal fluid pressure,[1–7,§] whereas other investigations have been unable to demonstrate this phenomenon.[¶,**,††] This ambiguity has spawned a variety of clinical recommendations[1,4,§] and considerable debate.[8,9]

The authors' interest in this problem heightened when a patient with a malignant brain tumor developed increased ICP after Sch was given for a biopsy operation (fig. 1). Because of this experience and previous evidence indicating that complete nondepolarizing neuromuscular blockade prevents the electrophysiologic changes associated with Sch,[10] we undertook this study both to determine the incidence of Sch-induced increases in ICP in neurosurgical patients and to investigate the impact of prior nondepolarizing neuromuscular blockade on increases in ICP induced by Sch.

Materials and Methods

Two groups of patients with brain tumors were studied (Group 1 = 13 patients; Group 2 = 6 patients). All patients were scheduled for elective craniotomy and were receiving dexamethasone, 20 mg po daily, preoperatively. Their ages ranged from 35–75 yr and preoperative computed tomographic (CT) scans of their heads indicated that all tumors were at least 3 cm in diameter. All had significant cerebral edema and most had a shift of midline intracranial structures. The protocol for this study was reviewed and approved by the institution's Human Investigation Committee, and written consent was obtained from each patient.

In Group 1, patients were studied in consecutive order. Seven patients were premedicated with glycopyrrolate, 0.2 mg im, and morphine sulfate, 0.1 mg · kg^{-1} im, 1 h prior to arrival in the operating room suite. The remaining patients in Group 1 were unpremedicated. The pa-

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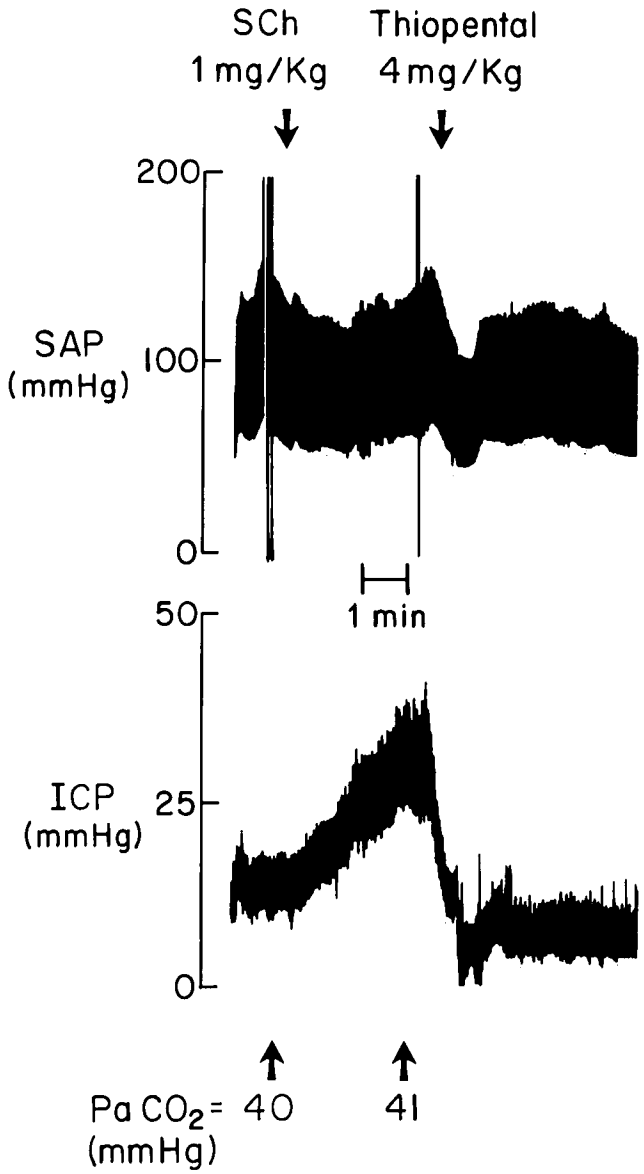

FIG. 1. Changes in intracranial pressure (ICP) and systemic arterial pressure after induction of anesthesia with thiopental and 70% nitrous oxide in a patient with a brain tumor. Despite controlled ventilation, an abrupt increase in ICP occurred after succinylcholine, 1 $mg \cdot kg^{-1}$, necessitating intravenous thiopental therapy. Pa_{CO_2} was essentially unchanged, and no other stimuli that might have caused an increase in ICP occurred during this time.

tients in Group 2 were specifically chosen for study because, based on our findings in Group 1 (see "Results"), their preoperative CT scans indicated that they would probably develop small increases in ICP following Sch. Their tumors tended to be relatively small (3–4 cm) with a relatively narrow (1–2 cm) band of surrounding edema causing minimal (5–10 mm) lateral shift of midline structures. Group 2 patients were brought to the operating room unpremedicated.

Under local anesthesia a peripheral venous and radial arterial catheter and subarachnoid bolt were inserted. All pressures were continuously transduced (Bentley® Model 800 transducers) and recorded (Brush® Model 440 recorder) with the zero reference point at the external auditory meatus. Neuromuscular blockade was monitored with a force displacement transducer (Grass® Model FT-10) measuring adductor pollicis twitch tension in response to supramaximal ulnar nerve stimulation at 0.15 Hz delivered for a duration of 0.15 ms *via* subcutaneously placed 25-gauge needles.

Anesthesia was induced with patients in the 15° head-up position with thiopental, 6 $mg \cdot kg^{-1}$ iv, and 70% nitrous oxide in oxygen. Ventilation was controlled by mask to maintain a constant end-tidal CO_2 concentration (Hewlett-Packard® Model 47310-A capnometer), and verified by repeated arterial blood gas determinations 1 min before and 3 min after Sch. When stable mean arterial blood pressure (MAP) and ICP were observed for one minute, Sch, 1 $mg \cdot kg^{-1}$ iv, was administered over 5 s, and the resultant changes in ICP, MAP, and heart rate (HR) were recorded until first return of neuromuscular twitch. At this time, thiopental 4 $mg \cdot kg^{-1}$ iv, was administered, the trachea was intubated, and controlled ventilation continued with nitrous oxide in oxygen until complete return of neuromuscular twitch.

In Group 1, vecuronium, 0.14 $mg \cdot kg^{-1}$, was given to induce 100% twitch tension depression and a second dose of Sch, 1 $mg \cdot kg^{-1}$ iv, was then administered. The corresponding changes in ICP, MAP, and HR were recorded for 3 min while minute ventilation and end-tidal CO_2 continued to be held constant. Vecuronium was chosen because of its minimal effects on both hemodynamics and ICP.[11]‡‡ In Group 2, treatment was identical except that no vecuronium was administered. Presence or absence of gross muscle fasciculations was noted after each dose of Sch by three independent observers.

Changes in cardiovascular parameters and ICP that were recorded during Sch-induced paralysis were compared with control values obtained either before induction of anesthesia or before Sch using repeated-measures analysis of variance. Fisher's Exact Test was used to compare the incidence of clinically significant increases in ICP (≥9 mmHg) observed before and after vecuronium. $P < 0.05$ was regarded as significant.

Results

Our observations in Group 1 are summarized in table 1, and figure 2 displays the frequency distribution of the

‡‡ Giffin JP, Cottrell JE, Schwiry B, Capuano C, O'Neill J, Hartung J: Intracranial pressure after ORG NC 45 (Norcuron) in cats (abstract). Anesth Analg 63:218, 1984.

TABLE 1. Intracranial Pressure (ICP), Mean Arterial Pressure (MAP), Cerebral Perfusion Pressure (CPP), Heart Rate (HR), and Arterial CO_2 Tension before and after Succinylcholine (Sch), Vecuronium, and a Second Dose of Sch in Group 1 Patients

		Before Vecuronium		After Vecuronium	
	Awake	1 Min before Sch Dose #1	3 Min after Sch Dose #1	1 Min before Sch Dose #2	3 Min after Sch Dose #2
ICP (mmHg)	12 ± 1	15 ± 1	20 ± 2*†	11 ± 1	12 ± 1
MAP (mmHg)	91 ± 4	87 ± 4	83 ± 3	79 ± 4†	73 ± 3†
CPP (mmHg)	78 ± 4	72 ± 3	63 ± 3†	68 ± 3†	61 ± 2†
HR (beats/min)	70 ± 3	78 ± 2	80 ± 2	78 ± 2	76 ± 1
PA_{CO_2} (mmHg)	34.0 ± 1.8	37.0 ± 1.5	37.2 ± 1.7	38.5 ± 1.7	38.0 ± 1.9

All values are mean ± SEM.
* $P < 0.05$ *vs.* values before Sch dose #1.
† $P < 0.05$ *vs.* awake control values.

peak increases in ICP among these patients. After the first dose of Sch, five of the 13 patients developed increases in ICP of 9 mmHg or more, changes which we felt to be clinically significant. While there was some variability with regard to the time of peak increase in ICP, in all cases this had begun by 1 min, the median time for peak increase was 3 min, and ICP remained elevated until return of muscle twitch. The time from Sch administration until first return of visible twitch was 8.7 min ± 0.4 (mean ± SE). When complete neuromuscular blockade with vecuronium preceded Sch, no patient sustained an increase in ICP as great as 9 mmHg ($P < 0.05$ *vs.* the incidence of ICP ≥ 9 mmHg after the first dose of Sch by Fisher's exact test), and the largest increase in ICP was only 3 mmHg.

All five patients who exhibited increases in ICP of 9 mmHg or greater with the initial dose of Sch showed no evidence of gross muscle fasciculations after Sch. In contrast, no patient who fasciculated in response to the initial dose of Sch sustained an increase in ICP of greater than 4 mmHg. Three patients who did not fasciculate also demonstrated only minor changes in ICP.

Among the five patients who developed increases in ICP of 9 mmHg or greater, four had malignant gliomas and one had a large meningioma. All had a wide rim of surrounding brain edema and a marked shift (>10 mm) of midline structures visible on CT scan. Among the patients who sustained small changes in ICP after Sch, only one had a malignant glioma and the remainder had nonglial tumors. CT scans showed minimal edema surrounding these tumors, and none had a lateral shift of midline structures larger than 5 mm. Thus, it appears that those patients with the greatest CT scan evidence of compromised intracranial compliance were the ones who sustained the greatest increases in ICP following Sch.

Succinylcholine had no impact on arterial pressure. However, MAP was significantly reduced after the second dose of thiopental plus vecuronium neuromuscular blockade (table 1). Cerebral perfusion pressure (MAP − ICP) was significantly lower than awake values 3 min after the first dose of Sch, due to both an increase in ICP and a decrease in MAP. It remained depressed after vecuronium due to a decrease in MAP. Vecuronium, however, was found to have no effect on ICP.

Figure 3 summarizes the changes in ICP that occurred after two doses of Sch in Group 2. Without intervening nondepolarizing blockade, small but significant increases in ICP occurred after both injections. In Group 2, as in Group 1, no significant change in cardiovascular parameters occurred in response to Sch administration.

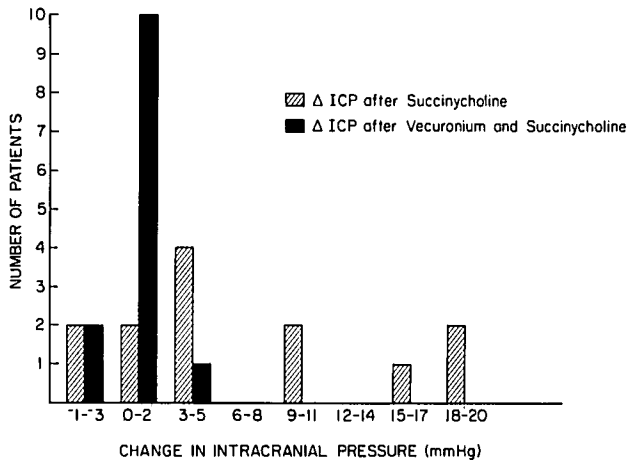

FIG. 2. Peak increases in ICP after succinylcholine, 1 $mg \cdot kg^{-1}$ iv, in Group 1. Initially, five of 13 patients had ICP increases of 9 mmHg or greater. After complete neuromuscular blockade with vecuronium, 0.14 $mg \cdot kg^{-1}$, one patient had an ICP increase of 3 mmHg, but no other patient's ICP increased more than 2 mmHg.

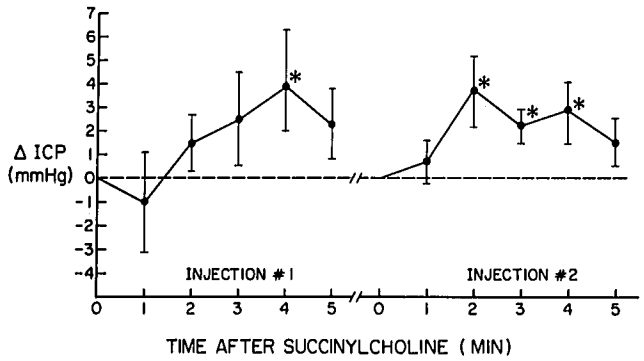

FIG. 3. Changes in ICP in Group 2 patients following two injections of succinylcholine, 1 $mg \cdot kg^{-1}$ iv, without intervening vecuronium paralysis. ICP increased each time succinylcholine was given. Asterisk indicates $P < 0.05$ *vs.* baseline ICP.

Discussion

Since the first report by Halldin and Wahlin in 1959,[6] the effect of Sch on intracranial or CSF pressure has been addressed in numerous studies.[1-7,§,¶,**] Most of these have demonstrated increases in ICP in response to Sch, although the magnitude of the change has been obscured by decreases in ICP induced by hyperventilation[1,5,7] and thiopental§ or confused with increases in ICP due to stimuli such as endotracheal intubation[1,2,7,12] or suctioning.[13]

In the present study we attempted to control or minimize factors other than Sch that would affect ICP. Thus, while MAP and ICP decreased after each dose of thiopental, we allowed these variables to return to baseline before Sch was administered. Data were obtained both before and after Sch during a steady-state nitrous-oxide–barbiturate anesthetic with ventilation controlled to maintain constant arterial CO_2 tension. External stimuli that might increase ICP[12] were either avoided or held constant during the study.

The mean increase in ICP observed after Sch in our study was nearly identical to that reported by Marsh *et al.* (5.2 mmHg ± 1.9 SE),§ and they, like we, noted that the patients who sustained the greatest increases in ICP did not fasciculate. However, the significance of this observation remains to be elucidated. Marsh *et al.*§ suggested that increased ICP following Sch may have been due to an increase in central venous pressure (CVP) occurring with the institution of controlled ventilation. In contrast, we employed controlled ventilation throughout the present study. Previous work done at our institution has demonstrated no direct impact of Sch on CVP during N_2O-O_2–barbiturate anesthesia with controlled ventilation,[14] and five of the patients in the present study who had CVP catheters in place sustained no change in CVP after Sch.

The impact of pretreatment with nondepolarizing muscle relaxants on Sch-induced increases in ICP has not previously been studied in a systematic fashion in humans. Examination of the tabular data from studies by both McLeskey *et al.*[1] and Shapiro *et al.*[12] reveals that ICP did not increase after a thiopental–Sch induction sequence when preceded by a 3 mg "defasciculating" dose of *d*-tubocurarine, whereas ICP did increase after endotracheal intubation. In patients without nondepolarizing pretreatment, Lewelt *et al.*[2] noted that ICP began to increase with the onset of fasciculations and then peaked with endotracheal intubation. Because none of these studies used each patient as his or her own control, it is not possible to determine if Sch was responsible for the increase in ICP. In the present study, however, we found that the same patients in Group 1 whose ICP initially increased in response to Sch sustained no change in ICP when Sch was given following nondepolarizing neuromuscular blockade. This difference most likely was caused by the nondepolarizing neuromuscular blockade because the patients in Group 2 sustained similar increases in ICP when Sch was given twice without intervening nondepolarizing blockade. Although the lower blood pressures noted after vecuronium paralysis might have resulted in improved intracranial compliance, we doubt that this was the cause of such a dramatic difference in response to Sch.

The neurophysiologic phenomena that cause an increase in ICP from Sch and prevent its occurrence following nondepolarizing neuromuscular blockade are not yet well understood. Recent work in a canine model by Lanier *et al.*[15] found that intravenous Sch induced EEG arousal immediately after muscle fasciculations and this was followed by a 77% increase in cerebral blood flow and a four-fold increase in ICP that peaked 3 min after Sch injection. In addition, Mori *et al.* have shown that Sch causes an EEG pattern consistent with cortical arousal during halothane anesthesia in humans.[10] They found that this effect occurs 60–90 s after Sch, lasts 6–8 min, and can be blocked by prior establishment of complete neuromuscular blockade. The findings of Lanier *et al.*[15] and Mori *et al.*[10] are thus strikingly compatible with our observed changes in ICP. It is our hypothesis, then, that patients with the most compromised intracranial compliance developed an increase in cerebral blood flow following Sch that was probably responsible for the observed increases in ICP.

Why should Sch cause an increase in cortical electrical activity with resultant increases in cerebral blood flow, cerebral blood volume, and ICP? At least one testable hypothesis is that this is induced by an increase in afferent neural traffic originating in muscle spindle receptors. Sch has been shown to induce an increase in afferent nerve firing from muscle spindles with a time-action curve that coincides with the duration of action of Sch, and this response is known to be repeatable with additional injections.[16] Furthermore, this activation of muscle spindle fir-

ing can be blocked by neuromuscular blockade with curare,[17] thus offering an explanation for why nondepolarizing neuromuscular blockade prevents the effects of Sch. While confirmation of this hypothesis will require further study in an animal model, it at least provides a possible explanation for the findings in the present study.

In summary, we found that Sch causes marked increases in ICP in some lightly anesthetized patients with intracranial neoplasms, particularly those with malignant gliomas. While the precise mechanism is unknown, our data indicate that previous institution of complete neuromuscular blockade by vecuronium prevents this phenomenon in those patients who are at risk.

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