Anesthesiology
75:669–672, 1991

Paraben Preservatives Do Not Increase Intracranial Pressure in Cats

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It has been hypothesized recently that succinylcholine-associated increases in intracranial pressure (ICP) are caused by the paraben preservatives contained in multidose vials. We tested that hypothesis in a standard feline model to determine the effect on ICP of equal-volume injections of preservative-free succinylcholine, succinylcholine with preservatives from multi-dose vials that contain both propylparaben and methylparaben, these preservatives alone at five times the dose contained in the succinylcholine, and normal saline. The preservatives alone increased ICP by 0.08 ± 0.08 mmHg (± standard error; not significant). Normal saline had no effect on ICP. Preservative-free succinylcholine and succinylcholine with preservatives increased ICP by 4.2 ± 0.10 and 3.8 ± 0.07 mmHg respectively ($P < 0.01$ compared to the preservatives alone and normal saline). The 99% upper confidence limit for the increase in ICP induced by the preservatives alone was 0.42 mmHg. This result suggests that parabens do not cause or substantially augment the ICP increase associated with succinylcholine administration. (Key words: Brain: intracranial pressure. Neuromuscular relaxants: succinylcholine. Preservatives: methylparaben; propylparaben.)

HAMILTON and coauthors recently hypothesized that succinylcholine-associated increases in intracranial pressure (ICP) are caused by the paraben preservatives contained in multidose vials.[1]

Paraben preservatives have been shown to relax guinea pig tracheal smooth muscle *in vitro*.[2,3] Subsequently, parabens were shown to vasodilate *in vitro* preparations of human pial arteries[4] and rat basilar arteries.[5] Hamilton and coauthors recently have extended these findings to guinea pig and dog basilar arteries, adding the speculation that "the use of these preservatives in intravenous solutions of some but not all commercially available brands of succinylcholine may contribute to the controversy regarding the effects of succinylcholine on cerebral blood flow and ICP both in patients and in experimental animals."[1]

We used an *in vivo* cat model to test the effect of succinylcholine with and without paraben preservatives as well as the effect of a high concentration of paraben preservatives alone, to see whether the vasodilatory effect attributed to the preservatives *in vitro* causes and/or augments the increase in ICP that has been attributed to succinylcholine administration *in vivo*.[6–15,**]

Materials and Methods

After obtaining approval from the Animal Care and Use Committee of State University of New York Health Science Center at Brooklyn, anesthesia was induced by spontaneous respiration of 70% nitrous oxide in oxygen with isoflurane at 1 ± 0.5 cat MAC (1.63%)[16] in six adult male mongrel cats. The cats weighed 5.9 ± 1.0 kg after being fasted for 8 h with water available *ad libitum*. (Variance is expressed as ± standard error throughout.) After tracheal intubation, anesthesia was maintained by mechanical ventilation with the same gas mixture, and isoflurane was adjusted within the stated range to keep mean arterial pressure at 110 ± 20 mmHg. Ventilation was adjusted to maintain normocapnia (end-tidal carbon dioxide tension 35–40 mmHg). Both end-expired carbon dioxide and anesthetic gases were measured by a Datex 254 Airway Gas Monitor. A warming blanket and overhead lamp were used to maintain normothermia (37.5 ± 0.5° C). The cephalic vein was cannulated to permit drug administration and fluid infusion at a rate of 4 $ml \cdot kg^{-1} \cdot h^{-1}$. A catheter was inserted into the femoral artery for blood pressure measurement, determination of heart rate and rhythm, and sampling of arterial blood gasses to ensure correlation between arterial carbon dioxide and end-tidal carbon dioxide tensions.

An 18-G spinal needle was inserted into the cisterna magna to measure changes in ICP, and the wound site was sealed with cyanoacrylate adhesive to stabilize the monitoring needle. ICP was continuously transduced from the level of the cisterna magna. A T-piece connector attached to the catheter permitted measurement of the cis-

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Received from the Department of Anesthesiology, State University of New York Health Science Center at Brooklyn, and the Cleveland Clinic Foundation, Cardiothoracic Anesthesia, Cleveland, Ohio. Accepted for publication June 24, 1991.

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** Artru AA: Succinylcholine-induced increases in CSF pressure are not affected by $PaCO_2$ or mean arterial pressure in dogs. Journal of Neurosurgical Anesthesiology 2:4–10, 1990.

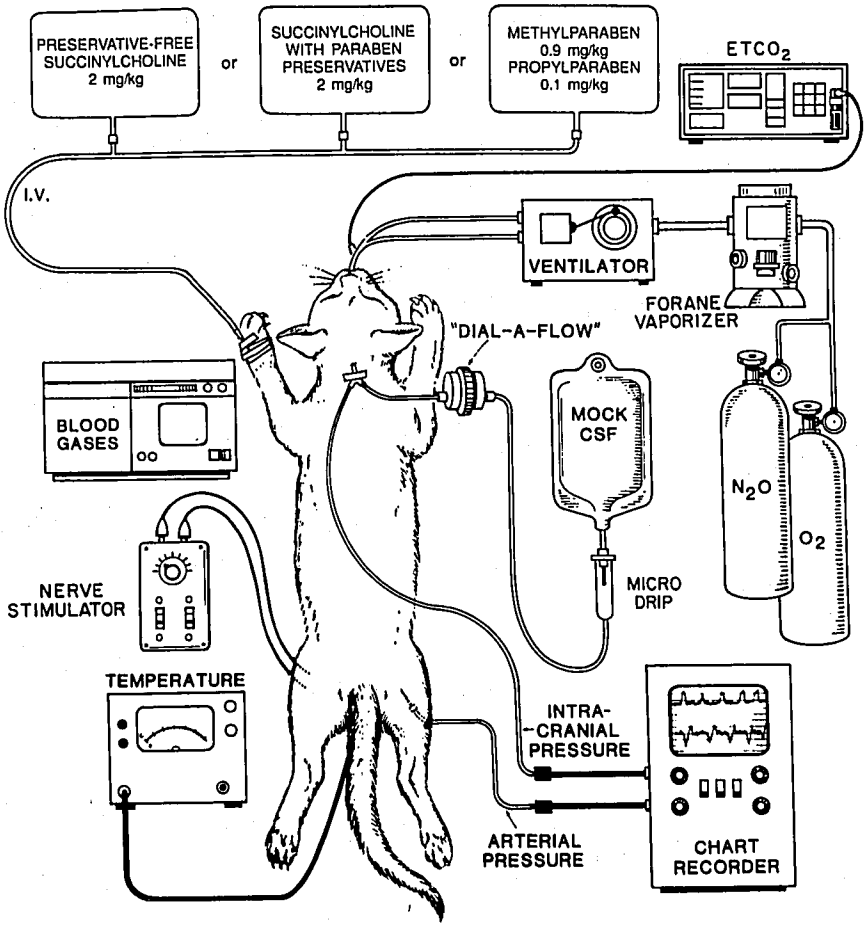

FIG. 1. Set-up for intracranial pressure model in cats. (See text and reference 6 for details.)

ternal ICP while allowing pressurization by microdrop infusion of mock cerebrospinal fluid (*p*H-adjusted lactated Ringer's solution). ICP measurements were accepted when the wave form pulsated 1–3 mmHg with each respiration. When properly sealed, this preparation facilitates increases of 20 mmHg almost immediately consequent to release of 10–20 microdrops into an administration set chamber. Thereafter, an infusion rate of 1 microdrop every 2–3 min maintains a stable ICP within the range of 28–30 mmHg (fig. 1). This model has been described previously in greater detail.[6]

The femoral nerve was identified, and needle electrodes were placed and attached to a nerve stimulator to ensure full train-of-four twitch height by hindlimb plantar flexion before injection of experimental drugs. This served to detect the onset and termination of the action of succinylcholine.

After the above-described preparation and parameters were stabilized, mock cerebrospinal fluid infusion was initiated to increase ICP to 25 ± 2 mmHg. We subsequently injected the following: 1) preservative-free succinylcholine 2 mg/kg (Anectine; containing 20 mg/ml succinylcholine), 2) succinylcholine with paraben preservatives 2 mg/kg (Quelicin; containing 20 mg/ml succinylcholine, 1.8 mg/ml methylparaben, and 0.2 mg/ml propylparaben), and 3) the paraben preservatives alone (0.9 mg/kg methylparaben and 0.1 mg/kg propylparaben in normal saline). All injections were 0.5 ml (dilutions with normal saline), and injection of each test drug was preceded by the injection of 0.5 ml normal saline. Each animal served as its own control for paired comparisons between baseline ICP (artificially elevated, preinjection) and ICP subsequent to injection of normal saline, preservative-free succinylcholine, preserved succinylcholine, and paraben preservatives alone.

TABLE 1. Test Drug Sequences in Each of Six Cats

Cat	Initial Sequence	Repeat Sequence
1	S SP MP/PP	MP/PP SP S
2	SP MP/PP S	S MP/PP SP
3	MP/PP S SP	SP S MP/PP
4	MP/PP SP S	S SP MP/PP
5	S MP/PP SP	SP MP/PP S
6	SP S MP/PP	MP/PP S SP

S = pure succinylcholine; SP = succinylcholine with preservative; MP/PP = preservatives alone (in normal saline).

In order to check for sequence effects and minimize the number of animals required, each cat was randomly assigned to one of each of the six logical sequences of administration of the three test drugs, with each individual sequence reversed and repeated in each cat (table 1). In order to limit cumulative mock cerebrospinal fluid infusion to 1.5–2.0 ml per animal across all six injections, infusion was discontinued between injections. Reelevated ICP was allowed to stabilize for 5 min before each injection. Thirty minutes elapsed between test injections, and all injections were followed by a 0.2 ml normal saline flush.

The two results for each test drug in each animal were averaged, giving a single value from each cat for each test parameter. Data were analyzed by analysis of variance followed by two-tail paired t tests and calculation of 99% confidence limits where appropriate. Sequence and temporal effects were checked by paired t tests between the first and second injection. In order to increase the probability of detecting such an effect, $P < 0.10$ was considered significant. All other statistical tests were considered significant at $P < 0.05$. All results are given as mean ± standard error.

Results

Paraben preservatives alone increased ICP by 1 mmHg after one injection in one cat, yielding an average increase of 0.5 mmHg in that animal and an overall mean increase of 0.08 ± 0.08 mmHg, from a baseline ICP of 25.4 ± 1 mmHg to a postinjection ICP of 25.5 ± 1 mmHg. The upper 99% confidence limit on that increase was 0.42 mmHg.

In contrast, preservative-free succinylcholine increased ICP by 4.2 ± 1 mmHg from a baseline ICP of 24.7 ± 1 mmHg to a postinjection ICP of 28.9 ± 1.4 mmHg, and succinylcholine with preservatives increased ICP by 3.8 ± 0.7 mmHg from a baseline ICP of 23.9 ± 0.2 mmHg to a postinjection ICP of 27 ± 0.8 mmHg. Normal saline had no effect (fig. 2). The difference between preservative-free succinylcholine and succinylcholine with preservatives was not statistically significant, but the difference between both preservative-free succinylcholine and succinylcholine with preservatives was significant compared to the preservatives alone ($P < 0.003$ and 0.01 respectively, subsequent to analysis of variance; $P < 0.002$).

No significant decrease in blood pressure occurred subsequent to the injection of test drugs or saline; however, a decrease in mean arterial pressure of 5.8 ± 2.4 mmHg after injection of the paraben preservatives alone almost reached statistical significance ($P = 0.058$). There were no significant temporal or sequence effects. Arterial carbon dioxide tension correlated well with end-tidal carbon dioxide tension throughout the experiment, and pH remained at 7.41 ± 0.03 and hemoglobin oxygen saturation remained greater than 98%.

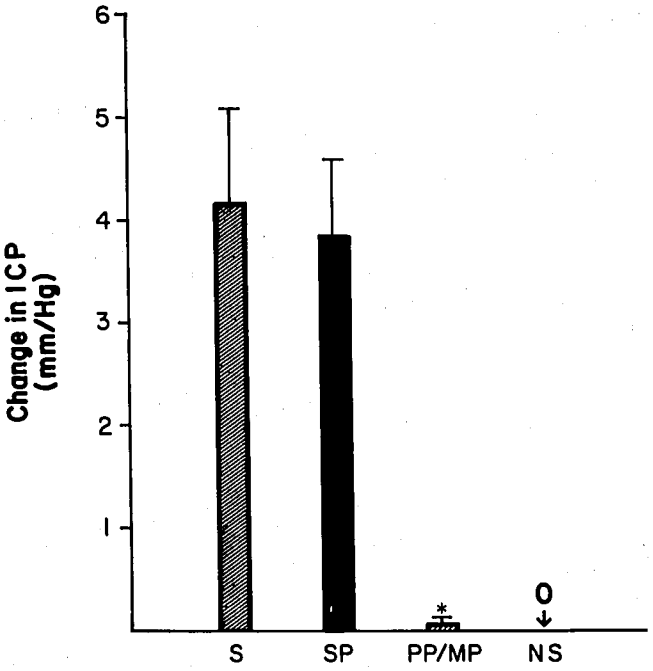

FIG. 2. Mean change ± SE in intracranial pressure (ICP) after injection of succinylcholine (S), succinycholine with preservatives (SP), preservatives alone (PP/MP), or normal saline (NS). *Difference significant from S and SP, $P < 0.003$ and 0.01 respectively; subsequent to ANOVA, $P < 0.002$. Normal saline had no effect.)

Discussion

Although paraben preservatives have been found repeatedly to cause vasodilation *in vitro*,[1–5] our *in vivo* model suggests that parabens do not cause the ICP increases associated with administration of paraben-containing injections of succinylcholine. This finding is consistent with Hamilton and coauthors' finding that "intravenous administration of clinically relevant doses of methylparaben and propylparaben do not increase CBF [cerebral blood flow]" in humans.[1] Our finding that parabens caused a small, transitory and tentative ($P < 0.058$) decrease in mean arterial pressure is also consistent with Hamilton and coauthors' *in vitro* result, suggesting that parabens have some systemic vasodilatory effect.

The succinylcholine-induced increases in ICP observed in this experiment were not as large as those observed in some previous laboratory studies,[7,8] including our own,[6] but are consistent with the magnitude of increase seen in other studies.[9,10,**] These discrepancies may be a consequence of different anesthetic backgrounds[8] and/or experimental protocols. Particularly critical in this regard is whether artificial elevations in ICP bring experimental

animals close to the steep portion of their intracranial volume/pressure elastance curve. A 4–5-mmHg increase in ICP is not of clinical concern when baseline ICP and intracranial elastance are normal†† and is only infrequently of concern in patients with elevated ICP (> 25 mmHg). However, in patients with elevated ICP and a cerebral midline shift,[15] obstructed venous outflow, and/or obstructed cerebrospinal fluid resorption, the increase in cerebral blood volume that can cause a 4–5-mmHg ICP increase in individuals with normal cerebral elastance can result in dangerously elevated ICP, aneurysm rupture, and/or brain herniation.‡‡

The finding that succinylcholine can elevate ICP independent of paraben preservatives and the finding that the preservatives alone have a negligible effect, in conjunction with Shirahase and coauthors' finding that pure succinylcholine constricts canine basilar arteries *in vitro*,[17] suggests that ICP increases associated with succinylcholine with or without preservatives are not due to direct cerebral vasodilation by either succinylcholine or the paraben preservatives. These findings, in turn, bolster Lanier and coauthors' hypothesis that succinylcholine elevates ICP indirectly, by stimulating muscle afferent activity and consequently cerebral metabolism, cerebral blood flow, and cerebral blood volume.[8,9,18]

Our finding that succinylcholine with and without preservatives consistently increases ICP whereas the preservatives alone do not, leaves intact the inference that pure succinylcholine is of as much concern as preserved succinylcholine when intracranial elastance is critically compromised.[15] More directly, our findings imply that the use of paraben preservatives in some commercially available brands of succinylcholine does not "contribute to the controversy regarding the effects of succinylcholine on cerebral blood flow and ICP both in patients and in experimental animals."[1]

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