

## Prevention of Succinylcholine Fasciculation with Local Anesthetics

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Fasciculations secondary to succinylcholine injection were prevented in surgical patients by pretreatment with adequate doses of procaine and lidocaine. Lidocaine was more effective in equal dosage. The protective effect did not appear to depend on circulatory factors or inhibition of the plasma cholinesterase system. The site of action appears to be at the myoneural junction, suggesting an effect on the acetylcholine system and presynaptic membrane.

ONE OF THE ACCOMPANYING effects of intravenously administered depolarizing muscle relaxants is fasciculation, associated in some patients with development of postoperative muscular pain,<sup>1,2</sup> increased intragastric pressure<sup>3</sup> and release of catecholamines.<sup>4</sup> Attempts have been made to minimize this effect by prior injection of nondepolarizing relaxing agents or by fluorinated substances (hexafluorenum).<sup>5,6</sup> In a clinical experience with intravenous procaine anesthesia, a common technique of general anesthesia in Argentina, fasciculations do not appear when succinylcholine was injected after procaine administration.<sup>7</sup> Since procaine as a substrate competes with succinylcholine for cholinesterase<sup>8</sup> this study was undertaken to compare its protective effect with that of lidocaine, an amide, which lacks significant anti-cholinesterase activity. The protective action encountered after single doses of procaine or lidocaine was independent of cardiovascular effects, blood enzymatic inhibition or central nervous system depression, but related to an effect at the myoneural junction.

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### Material and Methods

Two-hundred and twenty-five surgical patients without hepatic symptomatology, ranging in age from 12 to 72 years, were studied. These patients were divided into four basic groups.

**Group A—Control.** One-hundred patients were given thiopentone (3 mg./kg.) intravenously followed in three minutes by succinylcholine (1 mg./kg.).

**Group B—Intravenous Procaine.** Fifty patients were subdivided into five groups of 10 each. Three minutes following intravenous thiopentone (3 mg./kg.) administration they received procaine (2, 4, 6, 8 or 10 mg./kg.) intravenously. The duration of procaine administration was 3 minutes following which all groups were given succinylcholine (1 mg./kg.) intravenously.

**Group C—Intravenous lidocaine.** Fifty patients were treated in the same fashion as group B, except that lidocaine (2, 3, 4, 5 or 6 mg./kg.) was substituted for procaine.

**Group D—Intra-arterial injections.** Three minutes following intravenous thiopentone (3 mg./kg.) administration 25 patients received procaine (4 mg./kg.) intra-arterially. After an additional 3 minutes these patients received succinylcholine (1 mg./kg.) intravenously.

In all patients pulse, blood pressure and the ECG were monitored. Patients were observed for fasciculations particularly of the eyelids and extraocular muscles. The time between injection of succinylcholine and the appearance of peri-orbital fasciculation was recorded.

In 3 patients from group B (5 mg./kg. of procaine) and in 7 patients from group B (10 mg./kg. of procaine) a 10 ml. sample of heparinized venous blood was drawn immedi-

TABLE 1. Procaine and Lidocaine in the Prevention of Fasciculations Induced by Intravenous Succinylcholine

Groups	Number	Fasciculation	Movement Extremities	No Change	Effective Prevention (Per Cent)
Controls	100	100	22	0	—
Procaine (mg./kg.)					
2	10	10	2	0	—
4	10	10	1	0	—
6	10	8	1	2	20
8	10	4	—	6	60
10	10	1	—	9	90
Lidocaine (mg./kg.)					
2	10	10	1	0	—
3	10	10	2	0	—
4	10	7	1	2	20
5	10	4	—	6	60
6	10	—	—	10	100

ately prior to succinylcholine administration and the level of procaine and paraaminobenzoic acid was determined by a modification of the method of Banffi.<sup>9</sup>

### Results

In none of the 225 patients were significant changes ( $\pm 10$  per cent) in pulse rate or blood pressure observed. Two-hundred and twenty patients failed to demonstrate ECG changes during the study. After procaine administration 3 patients showed prolongation of the P-R interval and 2 patients showed occasional premature atrial contractions.

All patients in the control group (group A) demonstrated fasciculation and in 22 inco-ordinate movements of the extremities were noted.

The subgroups of group B pretreated with 2-4 mg./kg. procaine could not be distinguished from the controls (table 1). Fasciculations were markedly diminished, however, in the subgroups pretreated with procaine 6-8 mg./kg. and where absent in 9 of 10 patients pretreated with procaine 10 mg./kg.

In group C patients pretreated with 2-3 mg./kg. lidocaine could not be distinguished from the controls. Inhibition of fasciculation was observed in 2, 6 and 10 patients of the

subgroups pretreated with 4, 5 and 6 mg./kg. lidocaine, respectively.

Following intra-arterial procaine injection (4 mg./kg.) fasciculation with succinylcholine did not occur in the area perfused by the artery. Fasciculations did occur, however, in the opposite extremity.

The time between succinylcholine injection and development of peri-orbital fasciculations was not significantly different in the control and experimental groups where fasciculations occurred (table 2).

Blood procaine levels ranged from 0.20 mg./100 ml. to 1.93 mg./100 ml. (table 3).

### Discussion

Prevention of fasciculation secondary to succinylcholine administration by pretreatment of patients with intravenous local anesthetics has not been previously described. The mode of action of local anesthetics in preventing succinylcholine fasciculations as demonstrated in this study, can be predicated on one or more of the following modes of action:

(1) Modification of origin or transmission of nervous impulses in the cortex, brain stem or spinal cord.

(2) Variation in tissue perfusion secondary to effects on circulation.

(3) Enzymatic competition between the local anesthetic and succinylcholine.

TABLE 2. Circulation Time From Succinylcholine Injection to Fasciculation

Groups	Number	Circulation Time in Seconds							Means
		10	14	18	22	26	30	34	
Controls	100	3	32	39	18	5	2	1	18
Procaine*	50	2	19	13	8	3	1	—	19
Lidocaine*	50	2	17	19	4	2	—	—	17

\* In 4 patients of the procaine group and in 7 of the lidocaine group, the first sign of succinylcholine action was apnea, therefore circulation times was indeterminable.

(4) Qualitative alteration of the response of the myoneural junction to depolarizing agents.

*Action upon the Central Nervous System.* In animals, surgical severance of peripheral nerves does not prevent the appearance of fasciculation owing to succinylcholine.<sup>10</sup> Because of this a theory based on a cortical, brain stem, or spinal pharmacological action is not feasible and the site of action must be sought outside of the neuraxis.

*Circulatory Factors.* Clinical observations have shown fasciculation following slow intravenous infusion of succinylcholine to be markedly diminished or absent. Similar observations have been made in patients with severe cardiovascular depression, particularly in the presence of prolonged circulation time. Although the absence of fasciculation could be secondary to inadequate tissue perfusion, blood levels of succinylcholine have been found to decline precipitously thirty seconds following administration.<sup>11</sup> Enzymatic hydrolysis rather than altered distribution has been shown to be the cause of this rapid disappearance. This is substantiated by *in vitro* studies.

The similarity in circulation times and absence of significant changes in pulse rate, blood pressure and electrocardiographic tracings in both control and experimental patients contradicts a hypothesis based on an indirect action of the local anesthetic via cardiovascular depression.

*Enzymatic Mechanisms.* In 1953, Foldes<sup>8</sup> reported on the potentiation of succinylcholine paralysis by procaine hydrochloride in man. The mechanism of action was reported to be competition for plasma cholinesterase between succinylcholine and procaine. We do not believe that inhibition of the enzymatic mechanism can explain our results for the following reasons:

The total capacity of circulating cholinesterase for hydrolysis of procaine HCl in an average adult man is approximately 20 mg./minute.<sup>12</sup> However, with single doses of procaine as high as 280 mg. (4 mg./kg.) fasciculations were not inhibited following succinylcholine administration.

If the enzymatic activity of plasma cholinesterase is exhausted by procaine and suc-

TABLE 3. Procaine and Paraaminobenzoic Blood Levels After Injection of Procaine (5 mg./kg. or 10 mg./kg.)

Patient	Sex	Age (years)	Weight (kg.)	Dose (mg./kg.)	Procaine (mg./100 ml.)	Paraaminobenzoic Acid (mg./100 ml.)
1	F	37	41	10	0.50	0
2	M	18	51	10	1.00	0
3	M	72	72	10	0.80	1.50
4	F	38	72	10	0.53	0
5	M	54	65	10	1.93	0.64
6	M	47	75	10	1.37	0.31
7	F	41	76	10	0.41	0.17
8	M	54	65	5	0.93	0
9	M	47	75	5	0.88	0.12
10	F	41	76	5	0.20	0.11

cynylcholine is subsequently administered, the latter compound should reach the myoneural junction in greater quantities. However, the resultant increase in tissue concentration of the relaxant does not produce fasciculation.

Lidocaine hydrochloride, a local anesthetic which is not hydrolyzed by plasma cholinesterase, also protects the patient from succinylcholine fasciculation in adequate doses. These doses are smaller milligram than those required by procaine to effect the same inhibition.

McCaul<sup>13</sup> has reported that tetrahydroaminoacrine (a cholinesterase inhibitor that prolongs the action of succinylcholine) does not prevent succinylcholine induced fasciculations.

The results presented above therefore are not compatible with postulates based on central nervous system depression, circulatory depression, or enzymatic competition. We believe that the major factor in the inhibition of succinylcholine induced fasciculation by pretreatment with procaine or lidocaine is best explained by an *effective tissue level of the local anesthetic agent*. Intra-arterial administration of procaine HCl prevents the appearance of succinylcholine fasciculations in the area perfused by the artery, thus supporting this hypothesis. However, the site of action and mechanism involved remain to be determined.

In chronically denervated muscle (in which the Rouget plate is destroyed) no fasciculations are observed following succinylcholine injection.<sup>10</sup> This observation strongly suggests that the myoneural junction should be considered as a plausible site of action.

When an impulse traverses nerve, acetylcholine is eliminated gradually thus stimulating the receptor proteins of the myoneural junction.<sup>14</sup> This is the essence of neuromuscular transmission. Muscle relaxants act on the receptor sites of the myoneural junction and in the particular case of depolarizing agents "instead of acting like acetylcholine, seem to act, at first through acetylcholine."<sup>15</sup> Thus fasciculation may be due to sudden release of acetylcholine at the myoneural junction following the administration of succinylcholine. The administration of succinylcholine by slow intravenous infusion is not as apt to produce

fasciculation since the subsequent release of acetylcholine will be slower.

In a nonpretreated, normally polarized myoneural junction, the occurrence of fasciculation is related to the quantity and rate of succinylcholine administration. If an acetylcholine deficiency exists, however, succinylcholine will not produce fasciculation regardless of the quantity injected. This situation is observed in neonates<sup>16</sup> and in patients with myasthenia gravis in whom an alteration in the synthesis or release of acetylcholine is present.<sup>17</sup> In addition to congenital deficiencies, a temporary depletion of acetylcholine may be produced by prior release of stored acetylcholine or chemical agents which interfere with its release. The absence of fasciculation following a second dose of succinylcholine soon after the first may be related to depolarization of the myoneural junction or to insufficient reaccumulation of acetylcholine at the nerve endings.

Local anesthetic agents are known to act as mild myoneural blocking agents<sup>18</sup> by diminishing acetylcholine production<sup>19</sup> and by stabilizing the presynaptic membrane<sup>20</sup> thereby preventing its depolarization. Thus the parenteral administration of local anesthetic agents in addition to a direct action on the membrane may thereby prevent the massive liberation of acetylcholine secondary to succinylcholine administration and fasciculation will not occur.

### Conclusions and Summary

Procaine and lidocaine when administered in adequate doses prevented fasciculation secondary to succinylcholine injection. Lidocaine was more effective in equal dosage.

The protective effect did not appear to depend on circulatory factors or inhibition of the plasma cholinesterase system. The site of action appears to be the presynaptic place of the myoneural junction.

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**BLOOD VOLUME** Measurements of blood pressure, circulating blood volume and heart output of cells and plasma were made in cats anesthetized with chloralose and urethane following a sequence of small hemorrhages. Measurements were made only when the circulation had reached a relatively steady state, so that the changes observed were primarily a function of the volume of blood withdrawn. During the first part of the sequence arterial blood pressure was maintained by vasoconstriction. Haematocrit remained constant and a reduction of vascular volume equal to the blood volume bled took place. Thereafter arterial pressure and haematocrit fell. Trappings of cells and a shift of fluid into the circulation usually occurred. The blood loss tolerated until blood pressure began to fall varied among animals of similar weight and a plot of the reduction in circulating volume against the initial blood volume suggests a linear relationship. The maximum reduction in circulating volume during the normotensive phase is equal to the initial volume minus 41 ml./kg. The present experiment supports the idea of a "blood volume reserve" representing the maximum blood loss which can be accommodated by vasoconstriction. (Groom, A. C., Roulunds, S., and Thomas, H. W.: *Blood Volume and Tolerance to Blood Loss, J. Physiol.* 171: 49P (June) 1964.)