The Influence of Solvent on the Myoneural Effects of Intramuscular Succinylcholine

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DESPITE the relatively few publications [1, 2, 3] dealing with the intramuscular use of succinylcholine, this method of administration is being employed with increasing frequency, not only in infants and young children, but also in adults.[4] Because of this, a study was initiated to observe, under controlled conditions, the onset and duration of action and the incidence of side effects of intramuscularly injected succinylcholine. When preliminary studies indicated that the solvent had a considerable influence on the myoneural effects of intramuscularly injected succinylcholine, a study of this variable was also included in the planned investigation.

Material and Methods

The observations to be reported were made on 43 patients of both sexes whose ages ranged from 22 to 65 years and whose plasma cholinesterase activity was within normal limits. In addition, intramuscular succinylcholine was also administered to a patient with cirrhosis whose plasma cholinesterase level was about 38 per cent of the normal mean.

All patients, included in this study, were to undergo elective extraperitoneal operative procedures on the lower half of the body under subarachnoid or epidural block, not extending above the tenth thoracic dermatome. After the establishment of the regional block and the withdrawal of a blood sample for the determination of plasma cholinesterase activity,[5] the patients, premedicated with 100 mg. pentobarbital sodium, 100 mg. meperidine hydrochloride and 0.4 mg. scopolamine hydrobromide (all administered intramuscularly) were lightly anesthetized with thiopental sodium and nitrous oxide-oxygen. The details of the technique have been described previously.[6]

The patients were divided at random into four groups. After the level of general anesthesia was stabilized, control readings of respiratory rate and minute volume, pulse rate and blood pressure were made. The minute volume was measured with a Bennett or Draeger ventilation meter inserted on the inspiratory side of the anesthetic circuit. Respiratory tidal volume was calculated from the respiratory minute volume and rate. Subsequently, the members of each group received 4.0 mg./kg. succinylcholine chloride in a 10 per cent freshly prepared solution injected into the gluteal or deltoid muscle. The solvents used were: In group 1 (10 subjects), water; in group 2 (10 subjects) 0.9 per cent saline; in group 3 (11 subjects), water containing 300 U.S.P. units of hyaluronidase per milliliter; and in group 4 (12 subjects), saline containing the same amount of hyaluronidase. On occasion, groups 1, 2, 3 and 4 will be referred to as water, saline, water plus hyaluronidase, and saline plus hyaluronidase groups, respectively.

Respiratory rate and minute volume, pulse rate and blood pressure were again determined at 3, 6, 10, 15, 20, 25 and 30 minutes after the injection of succinylcholine. Whenever the tidal volume was below control value, assisted and, in case of apnea, controlled ventilation was used. Fifteen seconds before each respiratory measurement, however, assisted or controlled respiration was discontinued. The subjects were considered apneic when the ventilation meter indicated a tidal volume of less than 25 ml. The duration of the respiratory depression was defined as the time interval between the injection of succinylcholine

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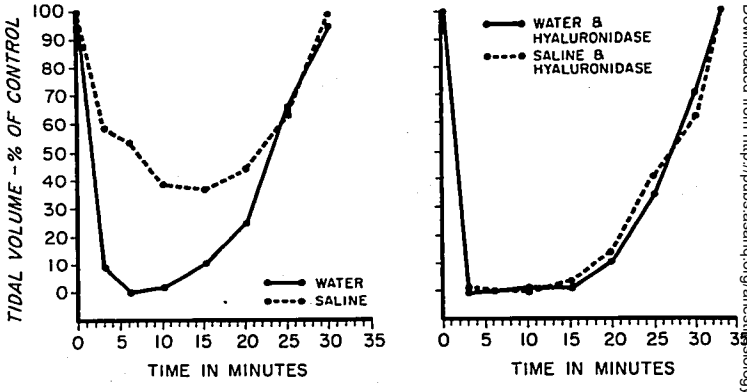

FIG. 1. Respiratory tidal volumes after the intramuscular administration of 4.0 mg./kg. succinlycholine in various solvents. The curves represent the means obtained in 10 to 12 subjects.

and the return of the respiratory tidal volume to control.

Whenever indicated by the clinical signs, additional small doses (25 to 75 mg.) of thiopental were administered to maintain a relatively even depth of anesthesia with little or no change in the respiratory rate.

Under the experimental conditions used, namely, eliminating the influence of the surgical reflexes on respiration by the regional block and diminishing that of hypercarbia by assisted or controlled ventilation, the spontaneous tidal volume of the subjects was a reliable, relative index of the neuromuscular effect of the intramuscularly injected succinylcholine.

Following the intramuscular administration of succinylcholine, the patients were observed for signs of muscular twitching and on the first postoperative day, they were questioned indirectly regarding muscle pain.

Results

The results of the experimental findings are summarized in table 1 and in figure 1. Fig-

TABLE 1. The Influence of the Solvent on the Respiratory Effects of Intramuscular Succinylcholine

	Solvent			
	Water	Saline	Water with Hyaluronidase	Saline with Hyaluronidase
Incidence of apnea	9 of 10	3 of 10	11 of 11	10 of 12
Onset of apnea (seconds)	155 ± 15.6* (n = 9)	253	106 ± 8.9 (n = 10)	138 ± 10.3 (n = 9)
Duration of apnea (seconds)	881 ± 93.4 (n = 9)	993	951 ± 103.0 (n = 10)	995 ± 87.0 (n = 9)
Duration of respiratory depression (seconds)	1,189 ± 126.4 (n = 9)	2,013 ± 237.0 (n = 10)	1,971 ± 85.0 (n = 10)	2,015 ± 105.0 (n = 9)

* Standard error.

ure 1 presents the mean tidal volumes of all subjects at the times indicated. It is evident from figure 1 that when succinylcholine was dissolved in saline, the depression of the tidal volume was less marked and maximum effect developed considerably later than when the solvent was distilled water. In agreement with this, as seen in table 1, apnea developed in 9 and 3 out of 10 subjects with water and saline solvents, respectively. In group 1, the mean onset of apnea (155 ± 15.6 seconds) was much faster than in the 3 subjects of group 2 in whom apnea developed. There was no difference in the duration of respiratory depression between these two groups. The addition of hyaluronidase to succinylcholine dissolved in water or saline tended to eliminate the differences observed between groups 1 and 2 (fig. 1 and table 1). In groups 3 and 4 apnea developed in 11 out of 11 and 10 out of 12 subjects, respectively. The onset of apnea in group 3 was significantly faster than in group 1 ($t = 2.7$), or group 4 ($t = 2.1$). The differences observed in the duration of apnea in the three groups were statistically not significant, and there was no significant difference in the duration of respiratory depression of the four groups. The differences in the onset and intensity of action of succinylcholine dissolved in water and saline are also evident in the respiratory tracings of representative cases. When the solvent was water (fig. 2), apnea developed in about 2 minutes and lasted almost 8 minutes. When the solvent was saline (fig. 3), apnea did not develop and the maximal respiratory depression, about 70 per cent of control, developed in 7.5 minutes.

In subjects with normal plasma cholinesterase values, there was no correlation between this parameter and the duration of apnea. A male cirrhotic patient, however, whose plasma hydrolyzed acetylcholine at the rate of 37.7 μM/ml. of plasma/30 minutes, instead of the normal mean rate of 114.4 μM for males,[7] showed a marked increase in both the duration of apnea (51 minutes) and respiratory depression (80 minutes).

Muscular fasciculations were observed in 2 patients of group 1. Postoperative myalgia was not observed in any subject.

Discussion

The intramuscular administration of 4.0 mg./kg. succinylcholine dissolved in water produced a consistent neuromuscular block. The mean onset and duration of apnea and duration of respiratory depression in our subjects, and in those of McDonald and Bryce-Smith,[1]

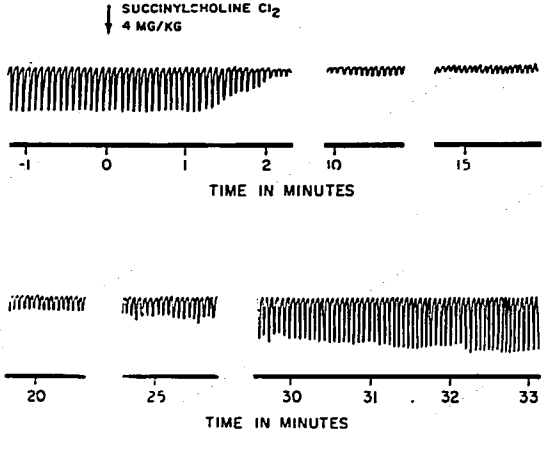

FIG. 2. The effect of intramuscular succinylcholine dissolved in water on respiratory tidal volume. Note the development of apnea in about two minutes.

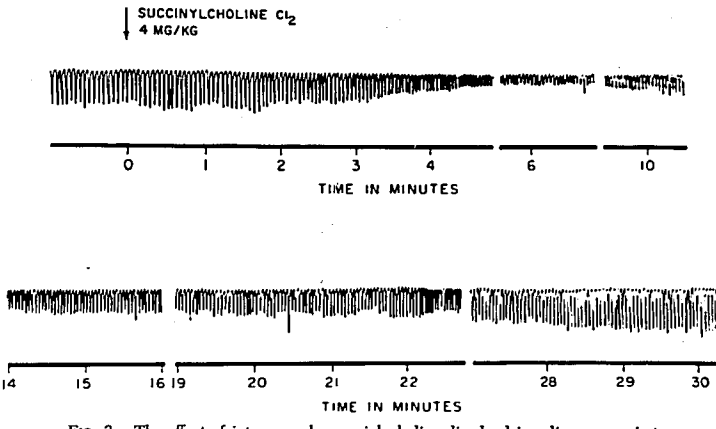

FIG. 3. The effect of intramuscular succinylcholine dissolved in saline on respiratory tidal volume. Note the absence of apnea.

receiving the same dose, were similar. In contrast, the effects of the same dose of succinylcholine when dissolved in saline were inconsistent and unpredictable. In the saline group, apnea developed in only 3 of 10 subjects. In 2 other subjects of this group, the intramuscular injection of succinylcholine had no measurable effect on the respiratory tidal volume. The apnea or maximal respiratory depression developed considerably later in this group than in the water group. It is probable that the slower onset and lower intensity of action of succinylcholine dissolved in saline was due to the inhibition of the absorbtion caused by the presence of sodium chloride. Because of the slower absorption and the relatively rapid hydrolysis rate of succinylcholine,[5] plasma levels necessary for the production of a total neuromuscular block were not achieved in most subjects of the saline group. This assumption is corroborated by the finding that when dissolved in 0.9 per cent saline, the absorbtion of local anesthetic agents from the cerebrospinal fluid was much slower than when the solvent was 6 per cent dextrose in water.[8] With saline solvent, the intensity of the resulting subarachnoid block was in most cases, not great enough to produce satisfactory operating conditions.[8]

The fact that the addition of hyaluronidase to the saline solution of succinylcholine speeded the onset and increased the intensity of the neuromuscular effect also favors the assumption that the effect of saline was caused by its influence on the absorption of succinylcholine.

Though the addition of hyaluronidase increased the speed of onset of the neuromuscular effects of intramuscularly injected succinylcholine with a 4.0 mg./kg. dose, the difference was not great enough to warrant its clinical application. In contradistinction, McDonald and Bryce-Smith[1] have demonstrated that with a smaller dose, 2.0 mg./kg., the addition of hyaluronidase accelerated the onset and increased the intensity of the neuromuscular block. The effects of 2.0 mg./kg. succinylcholine with hyaluronidase, except for a shorter duration of action, were similar to those observed after 4.0 mg./kg. succinylcholine alone. On the other hand, the neuromuscular effects of 2.0 mg./kg. succinylcholine without hyaluronidase were similar to those observed in the present study after 4.0 mg./kg. succinylcholine dissolved in saline and did produce satisfactory conditions for endotracheal intubation in the majority of cases. These findings indicate that the addition of hyaluronidase to intramuscularly injected succinylcholine is only

justified when neuromuscular block of great intensity, but of relatively short duration, is required. When more prolonged neuromuscular block is desirable, the addition of hyaluronidase to the larger dose of succinylcholine (4.0 mg./kg.) does not seem to offer any clinical advantages.

It is of interest that the duration of apnea and neuromuscular depression in a patient with cirrhosis and markedly decreased plasma cholinesterase activity was prolonged to about the same extent (three-fold) after the intramuscular injection of succinylcholine as after its intravenous use on other cirrhotic patients.[6] It was shown by Kalow and his associates that in the presence of atypical plasma cholinesterase,[9, 10, 11] the duration of the neuromuscular effect of intravenously injected succinylcholine was prolonged out of proportion to the decrease of the plasma cholinesterase activity. In such patients, the intravenous injection of 0.6 mg./kg. succinylcholine may cause apnea of as long as 4 hours duration.[12] It is reasonable to assume that the relationship between the intensity and duration of action of smaller intravenous and larger intramuscular doses found in normal subjects and in patients with low plasma cholinesterase activity due to liver disease, also holds true for subjects with atypical plasma cholinesterase. Consequently, if by chance, a 4.0 mg./kg. dose of succinylcholine were administered to such a subject, apnea of many hours duration might ensue. This hereditary anomaly[10] may also be encountered in infants and young children[12] in whom intramuscular succinylcholine is used most frequently. Consequently, anyone using succinylcholine by the intramuscular route should be cognizant of the possibility of encountering, in rare instances, apnea of excessively long duration and be prepared for the management of this complication.

Summary

Succinylcholine chloride, 4 mg./kg. in 10 per cent solution was administered intramuscularly to four groups of 10 to 12 subjects lightly anesthetized with thiopental sodium and nitrous oxide-oxygen. The succinylcholine was dissolved in group 1 in water, in group 2 in 0.9 per cent saline, in group 3 in water containing 30 U.S.P. units of hyaluronidase per milliliter, and in group 4 in saline containing the same amount of hyaluronidase.

When succinylcholine was dissolved in water, the onset of action was more rapid and its intensity greater than when the solvent was saline. In the water group, apnea lasting 881 ± 93.4 seconds developed in 155 ± 15.6 seconds in 9 out of 10 subjects. In the saline group, apnea lasting 993 seconds developed in 253 seconds in only 3 out of 10 subjects. There was no difference in the duration of the respiratory depression between the two groups.

The addition of hyaluronidase to the water solvent (group 3), except for the acceleration of the development of the maximal effect, caused no significant changes in the neuromuscular effects of succinylcholine. In contrast, the addition of hyaluronidase to the saline solvent markedly increased the neuromuscular effects of intramuscularly injected succinylcholine. Apnea developed in 10 out of 12 subjects of this group. The speed of onset of apnea (138 ± 10.3 seconds) became comparable to that observed in group 1.

It is suggested that the delayed onset and lesser intensity of action of intramuscularly injected succinylcholine dissolved in saline is due to the retardation of its rate of absorption and the prevention of the development of sufficiently high plasma concentrations of succinylcholine.

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INTRACTABLE PAIN While the perception of a painful stimulus takes place through fairly constant and well-known pathways, reaction to this perception is highly individual and is dependent upon the total experience of the patient. Posterior rhizotomy, chordotomy, and medullary tractotomy are indicated for interruption of pain pathways in selected patients. Frontal lobotomy is a useful adjunct where suffering of malignancy has not been relieved by an adequate chordotomy. Hypophysectomy has resulted in dramatic and almost immediate cessation of bone pain in 50 per cent of cases with widespread carcinoma of breast or prostate. *(Taren, J. A., and Kahn, E. A.: Surgical Relief of Intractable Pain, Surg. Clin. North Amer. 41: 1159 (Oct.) 1961.)*

HYPOTHERMIA A short preliminary hypoxia training of cats considerably increased their tolerance of deep hypothermia with a prolonged cardiac arrest and prevented severe morphological myocardial changes. Twenty per cent of similarly trained rats survived burn shock while all untrained controls died. In less severe burns, training prevented shock exhaustion and anemia, and considerably diminished the number of late deaths from burns. *(Gubler, E. V., Pinchuk, V. M., and Fenster, G. S.: Influence of Training in Hypoxia on Myocardial Changes and General Body Resistance in Deep Hypothermia and Severe Burns, Tretya Vsesoyuznaya konferentsiya patofiziologov. Tezisy dokladov (Moskva) 1960.)*

UREMIA Uremic plasma has a deleterious effect at several sites in the sequence of blood coagulation. Thrombocytopenia was commonly found in uremic patients, and in bone marrow examination a paucity of megakaryocytes as well as a striking erythroblastopenia was evident. Direct or indirect effects on the capillary wall were also observed. *(Kendall, A. G., and others: Hemorrhagic Diathesis in Renal Disease, Canad. M. A. J. 85: 405 (Aug. 19) 1961.)*