COMPARISON OF THE RESPIRATORY EFFECTS OF SUXAMETHONIUM AND SUXETHONIUM IN MAN

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IT HAS been suggested that the duration of apnea after the intravenous administration of suxamethonium (succinylcholine; SDCh) depends primarily on the plasma cholinesterase activity of the patient (1, 2, 3). Plasma cholinesterase activity was measured with acetylcholine (ACh) substrate in these studies. It had been reported previously (4) that the hydrolysis rates of acetylcholine, benzoylcholine, suxamethonium, and procaine do not change parallel with one another in plasmas obtained from healthy normal individuals. It seemed, therefore, worth while to reinvestigate the relationship between the duration of apnea obtained with a standard dose of suxamethonium and the hydrolysis rate of this compound in plasmas of patients with normal plasma cholinesterase activity, and also in patients with known liver disease. The respiratory effects and the hydrolysis rate of the diethyl derivative of suxamethonium, suxethonium (SEDCh), also were determined in the group of patients with normal plasma cholinesterase activity.

MATERIAL AND METHODS

The investigation was carried out on 29 patients with presumably normal plasma cholinesterase activity and in 18 patients with known liver disease. To exclude the possibility of the influence of reflexes, from the operative area on the duration of apnea (breath holding), patients undergoing various surgical procedures below the level of the twelfth thoracic segment, under subarachnoid or epidural block not extending above the tenth dorsal segment, were selected for this study. Patients were given premedication of 50 to 100 mg. of pentobarbital orally 90 to 120 minutes, and 0.4 to 0.6 mg. of atropine or scopolamine with 50 to 100 mg. of meperidine subcutaneously 45 to 60 minutes before induction of anesthesia. After the level of the regional block

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had been stabilized and the surgery started, light thiopental sodium anesthesia was induced and an oropharyngeal airway was inserted in the previously topically anesthetized pharynx. After the insertion of the airway, the anesthesia was maintained by the administration of a 70 per cent N_2O to 30 per cent O_2 mixture (5) and the intravenous injection of small doses of meperidine, administered prior to the determination of the control values of the respiratory rates and the tidal volumes. A Bennett ventilation meter was incorporated on the inspiratory side of the closed anesthetic circuit and respiratory rate and tidal volume were measured. After these became stabilized, either an 0.6 mg./kg. dose of suxamethonium dichloride (Anectine®) (4) or 1.2 mg./kg. dose of suxethonium dibromide (Brevidil E) (5) was injected intravenously in 30 seconds. The onset and the duration of apnea as well as the duration of respiratory depression were timed with a stopwatch. The duration of respiratory depression was measured by the time necessary for the return of the tidal volume to the value it had before the administration of suxamethonium or suxethonium. Twenty minutes after the administration of one of the two relaxants, the other relaxant was administered and similar observations were made. The hydrolysis rate of suxamethonium and suxethonium was determined in heparinized plasma, obtained from the experimental subjects before induction of anesthesia, with a modification of Warburg's manometric technique. The details of the method were described elsewhere (6). The plasma content of the vessels was 0.4 ml., the suxamethonium or suxethonium concentration was 2.2×10^{-2}M, and the bicarbonate concentration was 2.5×10^{-2} M. The volume of the system was 2 ml., its pH was 7.4, and temperature was maintained at 37 C.

In patients with known liver disease, subarachnoid block was not administered and the tests were carried out under light general anesthesia, as described, without the performance of any surgical procedure, or before the start of surgery. Premedication consisted of 0.4 mg. of atropine sulfate and the respiratory effects of suxamethonium alone were observed.

The hydrolysis rate of acetylcholine chloride also was determined by Warburg's method, and that of procaine hydrochloride was measured by a modification of Kalow's ultraviolet spectrophotometric technique (7) in the plasma of each patient.

RESULTS

Preliminary observations indicated that an 0.8 mg./kg. dose of suxethonium dibromide (equivalent on a molar basis to 0.6 mg./kg. suxamethonium dichloride) produced apnea in only 2 of 11 patients. In 1 patient, no apnea was produced by a 0.6 mg./kg. dose of suxamethonium dichloride. This patient, who was not included in the statistical analysis of our data, will be discussed later.

TABLE 1

COMPARISON OF THE ENZYMATIC HYDROLYSIS RATE AND THE RESPIRATORY EFFECTS OF SUXAMETHONIUM DICHLORIDE AND SUXETHONIUM DIBROMIDE

	SDCh-Cl₂*	SEDCh-Br₂†	ACh-Cl	Procaine.HCl
Enzymatic hydrolysis rate‡	3.0 ± 0.1§	4.8 ± 0.3	116 ± 4.0	0.7 ± 0.03
Onset of apnea in seconds	57.5 ± 2.7	56.0 ± 3.0	—	—
Duration of apnea in seconds	180.0 ± 9.0	76.0 ± 9.0	—	—
Duration of respiratory depression in seconds	234.0 ± 10.0	126.0 ± 39.0	—	—

* The dose of suxamethonium dichloride was 0.6 mg./kg.
† The dose of suxethonium dibromide was 1.2 mg./kg.
‡ μM hydrolyzed by 1.0 ml. of plasma in 30 minutes.
§ Standard error.

The intravenous administration of suxamethonium, although 30 seconds were taken for the injection of the 0.6 mg./kg. dose, was accompanied by slight but definite muscular twitching in almost every patient. The fasciculations observed after the 1.2 mg./kg. dose of suxethonium were less frequent and less marked.

The onset and the duration of apnea and the duration of the respiratory depression after the intravenous administration of 0.6 mg./kg. of suxamethonium or 1.2 mg./kg. of suxethonium in the 29 patients with normal plasma cholinesterase activity is presented in table 1. The average enzymatic hydrolysis rate of suxamethonium, suxethonium, acetylcholine, and procaine also are shown in this table. It is evident from table 1 that suxethonium is hydrolyzed by human plasma considerably faster than suxamethonium, and that both substrates are

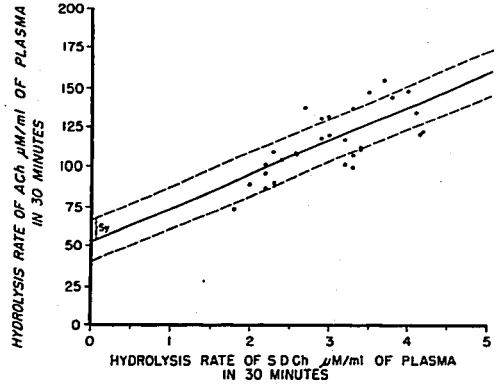

FIG. 1. Comparison of the hydrolysis rates of suxamethonium and acetylcholine in human plasmas.

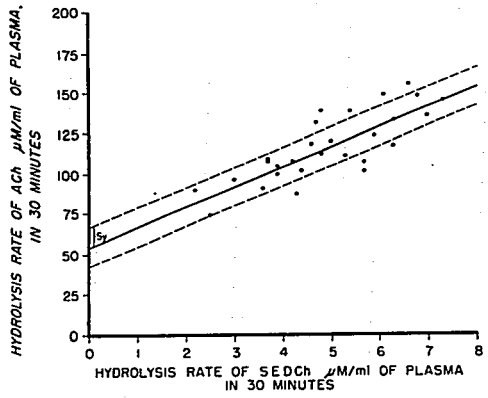

FIG. 2. Comparison of the hydrolysis rates of suxethonium and acetylcholine in human plasmas.

broken down much more slowly than acetylcholine but faster than procaine. The onset of apnea after intravenous administration was the same with suxamethonium and suxethonium. The duration of apnea and respiratory depression, however, was much longer after the 0.6 mg./kg. dose of suxamethonium than after the 1.2 mg./kg. dose of suxethonium.

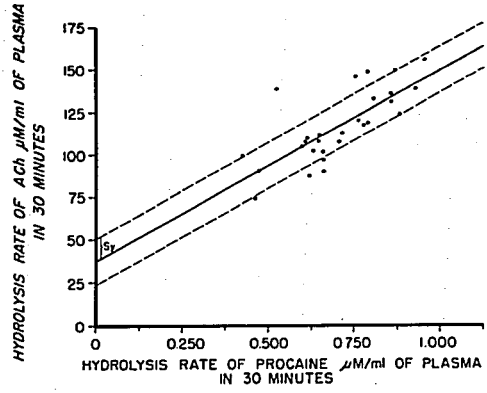

FIG. 3. Comparison of the hydrolysis rates of procaine and acetylcholine in human plasmas.

TABLE 2

CORRELATION BETWEEN THE ENZYMATIC HYDROLYSIS RATE OF VARIOUS SUBSTRATES AND THE DURATION OF APNEA CAUSED BY SUXAMETHONIUM DICHLORIDE AND SUXETHONIUM DIBROMIDE AND THEIR HYDROLYSIS RATE

Observations Compared	Correlation Coefficient*
Enzymatic hydrolysis of ACh-Cl vs. SDCh-Cl_2	0.75
Enzymatic hydrolysis of ACh-Cl vs. SEDCh-Br_2	0.81
Enzymatic hydrolysis of ACh-Cl_2 vs. procaine. HCl	0.75
Enzymatic hydrolysis of SDCh-Cl_2 vs. SEDCh-Br_2	0.77
Enzymatic hydrolysis of SDCh-Cl_2 vs. duration of SDCh-Cl_2 apnea	0.52
Enzymatic hydrolysis of SEDCh-Br_2 vs. duration of SEDCh-Br_2 apnea	0.34

* 1.0 represents perfect correlation.

Plotting the hydrolysis rate of acetylcholine against the hydrolysis rates of the other substrates used in this study (figs. 1, 2, 3) and calculating the correlation coefficients between the different groups of data (table 2), showed that there is a moderately good correlation (correlation coefficients 0.75 to 0.81) between the hydrolysis rates of the various substrates. Plotting the hydrolysis rates of suxamethonium and suxethonium against the reciprocal of the duration of apnea pro-

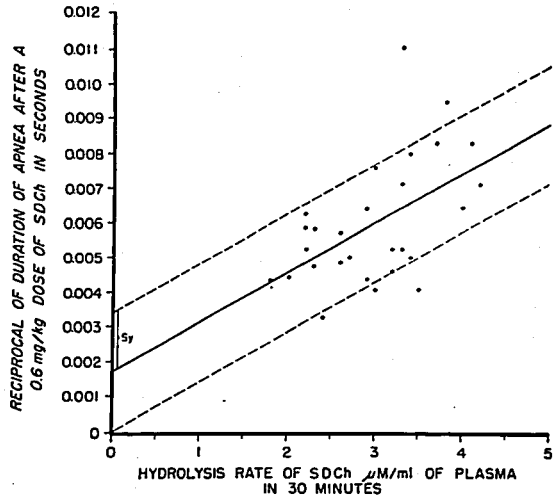

FIG. 4. Comparison of the hydrolysis rates of suxamethonium with the reciprocal of the duration of apnea after a standard dose of this compound.

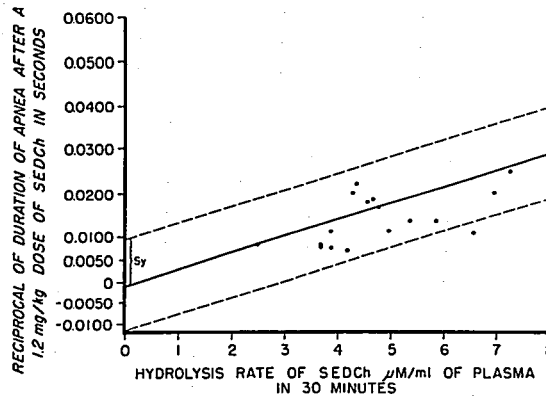

FIG. 5. Comparison of the hydrolysis of suxethonium with the reciprocal of the duration of apnea after a standard dose of this compound.

duced by an 0.6 mg./kg. dose of suxamethonium dichloride or a 1.2 mg./kg. dose of suxethonium dibromide (figs. 4, 5) showed poor correlation (correlation coefficients, 0.52 and 0.34, respectively).

In patients with liver disease, the plasma cholinesterase activity, measured by the hydrolysis rates of all 3 substrates, decreased in proportion to the severity of the pathological process. Lowest plasma cholinesterase activity was found in patients with advanced cirrhosis of the liver. The duration of apnea after the standard 0.6 mg./kg. dose of suxamethonium dichloride increased in proportion to the severity of the liver involvement. The increase in the duration of apnea, however, was less than the decrease of the plasma cholinesterase activity (table 3).

TABLE 3

COMPARISON OF THE ENZYMATIC HYDROLYSIS RATE AND THE RESPIRATORY EFFECTS OF SUXAMETHONIUM WITH THE HYDROLYSIS OF ACETYLCHOLINE AND PROCAINE IN NORMAL INDIVIDUALS AND PATIENTS WITH LIVER DISEASE

	Hydrolysis Rate (μM/ml. plasma/30 min.)			Duration of SDCh Apnea (sec.)
	SDCh	ACh	Procaine	
Normal individuals (29 cases)	3.0 ± 0.1*	116 ± 4.0	0.70 ± 0.03	180 ± 9
Patients with moderate liver disease (7 cases)	1.4 ± 0.2	59.0 ± 9.5	0.37 ± 0.08	348 ± 34
Patients with severe liver disease (11 cases)	0.8 ± 0.1	25.0 ± 5.7	0.17 ± 0.04	515 ± 40

* Standard error.

DISCUSSION

The findings presented confirm the observation of Stephen (8) that, in man, suxethonium is a less potent inhibitor of neuromuscular transmission than suxamethonium. An 0.8 mg./kg. dose of suxethonium dibromide equimolar to 0.6 mg./kg. of suxamethonium dichloride produced no apnea in 9 of 11 patients. One and a half times the equimolar dose of suxethonium (1.2 mg./kg.) produced apnea in all patients investigated, but the duration of the apnea was only about one half of the duration of the apnea caused by suxamethonium.

When given 20 minutes apart, the duration of apnea caused by suxamethonium or suxethonium did not seem to be influenced by the order in which the drugs were injected. This finding indicates that, when administered in 0.6 mg./kg. and 1.2 mg./kg. doses, respectively, no residual neuromuscular effect of either drug was discernible, in this group of patients, after 20 minutes.

Although the duration of apnea in the same individual was, in general, shorter after the more rapidly hydrolyzed suxethonium than after the more slowly decomposed suxamethonium, plotting the reciprocal of the duration of apnea caused by suxamethonium and suxethonium against their hydrolysis rates in the plasmas obtained from the same patients showed poor correlation. This observation suggests that, in patients with normal plasma cholinesterase activity, the duration of apnea observed after a moderate dose of suxamethonium or suxethonium not only depends on the enzymatic hydrolysis rate of these agents in the patient's plasma but also is influenced by other factors.

It has been discussed elsewhere (9) that the duration and the intensity of the neuromuscular effect of single, moderate, intravenous doses of suxamethonium depend (a) on the development of a primary distribution equilibrium between plasma and endplate and (b) on a secondary redistribution of suxamethonium from the endplates into the inactive tissue depots of the extracellular compartment. The role of plasma cholinesterase is restricted to the hydrolysis of suxamethonium that remains in the plasma after the development of the initial distribution equilibrium and to the breakdown of the suxamethonium that rediffuses from the endplate and the inactive tissue depots into the plasma as the concentration of suxamethonium falls there.

The relative importance of plasma cholinesterase activity becomes increasingly greater as the size of the single intravenous dose of suxamethonium is increased. The reason for this is that, after the development of the initial distribution equilibrium, the plasma concentration of suxamethonium will be greater the larger the initial dose. The same is true when suxamethonium is administered in continuous intravenous drip in concentrations capable of producing adequate surgical relaxation for prolonged periods. In such cases, the inactive tissue depots will be saturated rapidly and, since urinary excretion plays a relatively

minor role in the detoxification of suxamethonium (10), the determining factor in the rate of suxamethonium administration will be the plasma cholinesterase activity of the patient.

It is true that, in patients with markedly decreased plasma cholinesterase activity, the duration of apnea produced by identical mg./kg. doses of suxamethonium is longer than in normal individuals. The increase in the duration of apnea after the intravenous injection of a 0.6 mg./kg. dose of suxamethonium, however, was found to be less in 2 groups of patients, with moderate and severe liver damage, respectively, than the decrease in their plasma cholinesterase activity (table 3).

An important factor, capable of compensating to a considerable extent for a decreased or absent plasma cholinesterase activity, is the alkaline hydrolysis of suxamethonium. With the substrate concentration of 2.2×10^{-2}M employed in this study, the alkaline hydrolysis of suxamethonium at pH 7.4 amounted to 1.5 μM/ml. of plasma/30 min., or, in other words, to about 50 per cent of the average normal enzymatic hydrolysis rate of suxamethonium. In contrast with the enzymatic hydrolysis rate, there was no significant difference in the alkaline hydrolysis rate of suxamethonium in normal individuals and in patients with liver disease. The alkaline hydrolysis of suxamethonium is a second-order reaction, and, as such, is highly dependent on the substrate concentration. Since the plasma concentrations of suxamethonium encountered under clinical conditions are usually lower than the substrate concentrations used in the *in vitro* studies, the influence of the alkaline hydrolysis on the duration of apnea after the administration of moderate doses is less significant than it would appear from the results of the *in vitro* studies. On the other hand, in patients with low or absent plasma cholinesterase activity, the corrective influence of the alkaline hydrolysis of suxamethonium will become more important the larger the dose and consequently the higher the plasma concentration of suxamethonium reached.

As already mentioned, in previously reported studies on the relationship between plasma cholinesterase activity and sensitivity to suxamethonium, the plasma cholinesterase activity was determined with acetylcholine substrate (1, 2, 3). Since the alkaline hydrolysis rate of acetylcholine at pH 7.4 is considerably slower than that of comparable substrate concentrations of suxamethonium, the results of such comparison might not be representative of the true clinical picture. Furthermore, the present findings on the hydrolysis rate of various substrates by plasma cholinesterase as well as experiments already reported (4) indicate that, in different individuals, changes in the hydrolysis rates of these substrates do not parallel one another closely. It therefore is conceivable that, in some patients, the hydrolysis rate of acetylcholine can be relatively low while that of suxamethonium is normal or only slightly decreased. The reverse of this situation also might be encountered.

It has not been recognized generally that patients may be not only hypersensitive but also hyposensitive to suxamethonium. In a young female encountered in the course of this study, the hyposensitivity to suxamethonium was not related to an increased hydrolysis rate of this substrate in the patient's plasma. Although the enzymatic hydrolysis rate of suxamethonium in this patient's plasma was only 1.9 μM/ml./30 min. as compared with the normal average 3.0 μM/ml./30 min., no apnea developed after an 0.6 mg./kg. dose of suxamethonium and the apnea obtained with a second 0.6 mg./kg. dose administered 6 minutes later lasted only 130 seconds instead of the normal average of 180 seconds.

The findings of the present study indicate that variation in the hydrolysis rate of suxamethonium in the plasma of patients with a normal range of plasma cholinesterase activity does not explain the differences observed in the duration and the intensity of the neuromuscular effects of this compound. Observations made on patients with low plasma cholinesterase activity caused by severe liver damage showed that abnormally low plasma cholinesterase activity will markedly prolong the duration of apnea caused by standard doses of suxamethonium. However, alarmingly prolonged apneas previously reported (11, 12, 13) after single doses of suxamethonium were not encountered in any of these patients. It therefore is evident that this disturbing complication cannot be explained by low plasma cholinesterase activity alone. The possibility cannot be excluded that pathologically increased affinity of the cholinergic receptors to suxamethonium, or some other mechanism that prevents the redistribution of suxamethonium to the inactive tissue depots, is responsible for this phenomenon. It is conceivable that, as previously suggested (14), the sensitivity of the endplate to depolarization by suxamethonium may change under pathological circumstances and suxamethonium will act not as a "depolarizing" but rather as a "nondepolarizing" neuromuscular blocking agent. Indirect evidence in favor of this assumption is supplied by reports that prolonged apnea caused by suxamethonium could be terminated by the administration of neostigmine (15, 16).

SUMMARY

Suxamethonium dichloride administered intravenously in 0.6 mg./kg. doses produced apnea averaging 180 ± 9 seconds in 29 patients with a normal range of activity of plasma cholinesterase. Suxethonium dibromide in equimolar doses (0.8 mg./kg.) produced no apnea in 9 of 11 patients. In 1.2 mg./kg. doses, the average duration of apnea produced by suxethonium dibromide was only 126 ± 39 seconds. The average rate of enzymatic hydrolysis of suxamethonium was 3.0 ± 0.1 and that of suxethonium 4.8 ± 0.3 μM/ml. plasma in 30 minutes. The duration

of action of the more rapidly hydrolyzed compound, suxethonium, is shorter than that of the more slowly hydrolyzed suxamethonium in individuals with a normal range of activity of plasma cholinesterase. There was no close correlation, however, in normal individuals between the rate of enzymatic hydrolysis of either compound and the duration of apnea. No excessively prolonged apnea was encountered in a group of patients with a low activity of plasma cholinesterase caused by liver disease. It is concluded that the alarmingly prolonged apneas reported after suxamethonium cannot be explained satisfactorily by a low activity plasma cholinesterase alone.

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