The Relation Between Plasma Cholinesterase and Prolonged Apnea Caused by Succinylcholine

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The widely used muscle relaxant, succinylcholine dichloride (succinylcholine chloride) is hydrolyzed by plasma cholinesterase relatively rapidly to succinylmonocholine and choline. Subsequently, succinylmonocholine is hydrolyzed by the same enzyme to succinic acid and choline considerably more slowly. The primary breakdown product, succinylmonocholine, also has considerable neuromuscular activity. On a milligram kilogram basis, it is about one-twentieth as active as succinylcholine.

It had been suggested that the prolonged apnea encountered after the use of succinylcholine is the result of low plasma cholinesterase activity. Although the duration of apnea after identical or similar doses of succinylcholine was more prolonged in subjects with low plasma cholinesterase levels, it was shown that even in subjects with severe liver disease, who had extremely low plasma cholinesterase activity, the duration of apnea after 0.6 mg. kg. doses was prolonged only threefold, from 180 ± 9 to 515 ± 10 seconds. Furthermore, the intravenous administration of concentrated, purified human plasma cholinesterase had little or no effect on the course of prolonged apnea caused by succinylcholine and prolonged apnea was also encountered in patients whose plasma cholinesterase activity was within normal limits. On the basis of this experimental evidence, it was concluded that quantitative changes in plasma cholinesterase activity are not responsible for the excessively prolonged apneas occasionally encountered after succinylcholine.

Investigating the causes of excessively prolonged apneas encountered in mental patients after the intravenous administration of conventional doses of succinylcholine, Kalow and his associates discovered the existence of an "atypical" type of plasma cholinesterase. The activity of this enzyme was both quantitatively and qualitatively different from that of the plasma cholinesterase present in normal subjects. Plasmas containing atypical cholinesterase hydrolyzed various choline esters about two to four times more slowly than plasmas of normal subjects. Furthermore, determination of the Michaelis constants of the various substrates revealed that their affinity to the atypical enzyme was 1.4 to 6.0 times less than to the normal enzyme.

More information was obtained on the properties of the atypical enzyme by comparing the effects of dibucaine hydrochloride (dibucaine; Nuercaine) and various other inhibitors on the hydrolysis of benzoylcholine chloride (benzoylcholine) by normal and atypical plasma cholinesterase. Kalow and Genest found that a 10⁻⁶ M concentration of dibucaine, which inhibited the hydrolysis of benzoylcholine by normal plasma cholinesterase by 70 per cent or more, caused a less than 20 per cent inhibition of the activity of the atypical enzyme. They termed the percentage inhibition caused by dibucaine the "dibucaine number" (D.N.). Subsequently, Kalow and Davies also demonstrated that with the exception of the organo-phosphate-type inhibitors, e.g., di-isopropyl fluorophosphate and tetraethyl pyrophosphate, all other inhibitors of plasma cholinesterase had less effect on the atypical than on the normal enzyme. Two
bispotassium compounds, decamethonium bromide, decamethonium iodide, and succinylcholine were particularly weak inhibitors of the atypical esterase. The relationship between the inhibitory effect exerted on the atypical and normal enzyme for twelve other compounds investigated by these authors could be expressed by the exponential equation $E = E_0 \frac{[E_{	ext{atypical}}][E_{	ext{normal}}]}{[E_{	ext{atypical}}] + [E_{	ext{normal}}]}$, or in other words the difference between the effect on the atypical and normal enzyme increased with increasing potency of the inhibitors.

Further differences were noted by Kalow, in the properties of the typical and atypical cholinesterases from observing the effects of various buffers and activators. Their electrophoretic studies indicated, however, that despite the significant differences in their kinetic properties, the net electrical charges of the typical and atypical enzymes were so similar that they could not readily be separated.

Study of the sera of several thousand healthy subjects and hospitalized patients revealed that based on the D.N. the population as a whole could be divided into three unequal groups: In about 97 per cent of the sera studied the D.N. was 70 or more; in about 3 per cent it was between 70 and 10; and in about 0.03 per cent (1 in 2,820) it was 20 per cent or less. Investigation of the relatives of subjects who had atypical plasma cholinesterase revealed that the atypieity of this enzyme is an inherited trait. Kalow and Staron explained the genetic theory of the three phenotypes with D.N. of above 70, between 70 and 10, and below 20 by the assumption of the existence of two, non-dominant, allelic, autosomal genes symbolized by $A$ and $B$, respectively. The typical gene is $A$ and individuals with two such genes ($AA$) have normal plasma cholinesterase with D.N. higher than 70. Individuals with two atypical genes ($BB$) have atypical plasma cholinesterase with low activity and D.N. of 20 or less. Finally, subjects with one typical and one atypical gene ($AB$) have a mixture of the typical and atypical enzymes, with intermediate plasma cholinesterase activity and D.N. between 70 and 10.

Later Kalow modified somewhat the interpretation of the D.N. and now considers that D.N. above 71 represents normal homozygotes with typical plasma cholinesterase. D.N. below 30 is indicative of abnormal homozygotes with atypical esterase and D.N. between 71 and 30 are characteristic of heterozygotes with mixtures of the two esterases.

The existence of the two types of enzymes was recently confirmed by Liddell et al., who were able to separate, by column chromatography or paper electrophoresis, two distinct varieties of cholinesterase from plasma of heterozygotes. The first fractions obtained by either of the two methods represented about 30 per cent of the total activity and had D.N. of 20 to 24. The later fractions represented about 70 per cent of total activity and had D.N. of 79 to 89. Only one area of activity could be obtained from plasma of typical or atypical homozygotes. Separation of mixtures of plasma of typical and atypical homozygotes, however, resulted in a distribution similar to that found in plasma of heterozygotes.

Familial occurrence of low plasma cholinesterase activity suggesting inheritance was described by Forbath and associates in 1953 and by Allot and Thompson and Lehmann and Ryan in 1956 before the discovery of the atypical plasma cholinesterase had been reported by Kalow and his associates. It is probable, however, that these cases as well as those reported by Lehmann and Simmons in 1958, in whom D.N. were not determined, also were atypical homozygotes and heterozygotes.

The theory of two allelic autosomal genes, however, did not offer satisfactory explanation for all the genetic findings encountered in families of patients in whom succinylcholine-induced prolonged apnea was associated with the presence of atypical plasma cholinesterase... Kalow and Staron suggested that these discrepancies could be explained with the assumption of several different "normal" genes ($A_A, A_B, A_C, A_D$) each capable of producing typical plasma cholinesterase but at variable rates. According to them, a gene ($A_A$) may be encountered, which produces plasma cholinesterase at zero rate. With this expanded theory the various findings related to the inheritance of atypical plasma cholinesterase could be explained satisfactorily. Recently, Liddell and associates encountered a...
Table 4: Patients with Normal Plasma Cholinesterase Who Developed Apnea after Succinylcholine

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Duration of Apnea (min)</th>
<th>Rate of Hydrolysis of Succinylcholine (nmol/mg x min⁻¹)</th>
<th>Rate of Hydrolysis of Succinylcholine (nmol/mg x min⁻¹)</th>
<th>Rate of Hydrolysis of Phosphatidylcholine (nmol/mg x min⁻¹)</th>
<th>Rate of Hydrolysis of Phosphatidylcholine (nmol/mg x min⁻¹)</th>
<th>Rate of Hydrolysis of Phosphatidylcholine (nmol/mg x min⁻¹)</th>
<th>Rate of Hydrolysis of Phosphatidylcholine (nmol/mg x min⁻¹)</th>
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<td>56</td>
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<td>78</td>
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<td>83</td>
<td>56</td>
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<td>62</td>
<td>91</td>
<td>76</td>
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</table>

Normal values for the hydrolysis rates and for the percentage inhibition are presented in tables 2 and 3, respectively.

- Substrate concentration
- Inhibitor concentration
- 2-hydroxy-3-phenylbenzyl trimethylammonium bromide dimethylethermate

Subject who developed prolonged apnea after succinylcholine whose plasma cholinesterase activity was zero. Genetic studies of her family revealed that she was a homozygote (A/A) for the “silent” gene.

In addition to those already discussed, other variants of plasma cholinesterase had also been encountered. Harris and Whittaker, described a type of plasma cholinesterase with a normal D/N, but a resistance to inhibition with sodium fluoride. Lehmann et al., encountered one family where in five of six children of a seemingly normal homozygote and heterozygote the plasma cholinesterase level was the same as in atypical homozygotes, but the D/N was between that of atypical homozygotes and heterozygotes.

Stimulated by the publications of Kalow and his associates, 11 12 13 14 15 since 1957 we have investigated the plasma cholinesterase activity of patients, both from our own clinical material and from those referred to us, 8 who developed prolonged apnea after conventional doses of succinylcholine. Whenever possible, plasma samples obtained from the family members of the patients were also studied. The purpose of this publication is to present our findings and the interpretation thereof.

8 We are indebted to Drs. J. J. Doolakian (Iowa City, Iowa), F. A. Edgar, Jr. (Greenberg), E. T. Kibler (Los Angeles), N. Y., J. H. March, W. McDade, R. D. Patterson (Pittsburgh), F. L. G. Martin (New York), L. F. Schweiss (St. Louis, Mo.), and W. N. Walker (Bridgewater, W. Va.), who provided us with plasma samples from their patients and from relatives of these patients.

Material and Methods

Twenty patients in whom apnea lasting from 23 to 360 minutes developed after the intravenous administration of 20 to 60 mg, single doses or the continuous infusion of 100 to 400 mg, of succinylcholine were studied. There were 11 male and nine female patients in this series, their ages ranged from 6 to 38 years.

Two to three days postoperatively, 15 to 20 ml of blood was withdrawn from the antecubital vein with a dry syringe and mixed immediately with 0.4 ml of 50 mg, ml heparin solution in a test tube. The blood was centrifuged immediately and the plasma removed. The plasma samples obtained from other clinics were frozen immediately and transported packed in dry ice. With one exception all plasma samples mailed were received in frozen state. Plasma samples from our own patients were studied within 48 hours after their withdrawal, and all tests with the samples mailed to us were also completed within 48 hours after their receipt. Preliminary studies indicated that under these circumstances little change occurred in plasma cholinesterase activity and, as also reported by Kalow and Staron, 12 there was no change in D/N. between the withdrawal of the blood and the completion of the testing.

The enzymatic hydrolysis rate of acetylcholine chloride (acetylecholine), succinylcholine and butyrylcholine chloride (butyrylecholine) were determined with Ammon’s modification.
of Warburg's manometric method and that of benzyloxylcholine and procaine hydrochloride (procaine) by a modification of Kabow's ultraviolet spectrophotometric procedure. Details of both methods have been published elsewhere.

The inhibitory effect of 10 $\mu$M succinylcholine on the hydrolysis of benzyloxylcholine was also measured. All determinations were carried out in duplicate at pH 7.4 and 37 °C. Correction was made for nonenzymatic hydrolysis. With some specimens, because of the lack of adequate amounts of plasma, not all tests were performed. The enzymatic hydrolysis rates of benzyloxylcholine and procaine, however, were observed on all and the dibucaine number was determined in all but one plasma.

Investigation of the plasma cholinesterase activity was also carried out on two to seven members of the families of six patients in whom atypical plasma cholinesterase was encountered.

### Table 2. The Hydrolysis Rates of Various Substrates by Atypical Plasma Cholinesterase of Patients Who Developed Prolonged Apnea after Succinylcholine

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age and Sex</th>
<th>Dose of Succinylcholine</th>
<th>Duration of Apnea</th>
<th>Atypical Cholinesterase Activity</th>
<th>Succinylcholine</th>
<th>Dibucaine</th>
<th>Phenyldiamine</th>
<th>Phenyldiamine</th>
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<td>90</td>
<td>205</td>
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### Results

Of the 20 patients who reacted with prolonged apnea to 20 to 60 mg, single doses or to the intravenous infusion of 100 to 400 mg, of succinylcholine, four, anesthetized with thiopental sodium, nitrous oxide-oxygen and meperidine hydrochloride (Demerol) or alphaprodine hydrochloride (Nisentil), were found to have normal plasma cholinesterase activity. The hydrolysis rates of the various substrates, as well as the inhibition of the hydrolysis of benzyloxylcholine by the various inhibitors, including dibucaine, were within normal limits (table 1) in these four patients. The administration of narcotic antagonists, deliberate hyperventilation or stimulation of the tracheal mucosa with a suction catheter inserted through the endotracheal tube failed to elicit spontaneous respiration. When spontaneous respiration was re-established 30 to 75 minutes after the intravenous administration of 20 to 40 mg of succinylcholine, the respiratory tidal volume increased gradually, as usually seen.
with the termination of the effect of neuromuscular blocking agents.

The hydrolysis of the various substrates by the plasma of patients with prolonged apnea who had atypical plasma cholinesterase according to Kalow’s criteria are presented in Table 2. In subsequent tables and in the text patients will be referred to by their case numbers. It is evident from this table that although all substrates were hydrolyzed more slowly by the atypical than by normal plasma, the reduction of the hydrolysis rate of procaine was greater than that of other substrates. Of the 16 patients with atypical plasma cholinesterase, five did not hydrolyze procaine at all and, with four exceptions, the rate was less than 25 per cent of the normal rate in the other eleven. This can be seen more clearly in Table 3, where the ratios of the hydrolysis rates of the different substrates by atypical and normal plasma are presented. It is evident from this table that this ratio, both for men and women, is lowest with procaine.

The inhibitory effect of 10⁻⁴ M dibucaine, 10⁻⁵ M neostigmine bromide (neostigmine; Prostigmine), 3.3 x 10⁻⁶ M RO2-0683 (2-hydroxy-3-phenylbenzyl) trimethylammonium bromide dimethylcarbamate) and 3.3 x 10⁻³ M succinylcholine on the hydrolysis of benzylcholine by atypical plasma obtained from patients with prolonged apnea is shown in Table 4. The percentage inhibition caused by 10⁻⁴ M dibucaine on the hydrolysis of benzylcholine (D.N.) was below the normal limit of 71 in every plasma tested. The reduction in the inhibitory effect of the three other compounds was even greater than that of dibucaine.

Of the 16 patients with atypical plasma cholinesterase who developed prolonged apnea, 12 were atypical homozygotes and four were heterozygotes. The homozygotes included two pairs of siblings. In both these pairs the second siblings were given succinylcholine without any investigation of their plasma cholinesterase activity despite the fact that the first ones developed prolonged apnea after usual doses of succinylcholine.

Of the 21 members of the six families of patients with atypical plasma cholinesterase investigated (Table 5), judged by the D.N. and the hydrolysis rates of the various substrates, 1 out of 7, 1 out of 6, 2 out of 3, 1 out of 2, 3 out of 4, and 1 out of 2 members of the families of patients numbered 1, 8, 9, 11, 14 and 16 (see Table 2), respectively, had atypical esterase in their plasma. The D.N. indicates that of the patients whose families were investigated, numbers 1, 9, 11 and 16 were atypical homozygotes and number 11 was a heterozygote. Judging from the hydrolysis rates of various substrates, patient 8, whose D.N. was not determined, was probably also an atypical homozygote.

**Discussion**

The fact that four out of 20 patients who developed prolonged apnea after relatively small doses of succinylcholine had normal plasma cholinesterase activity indicates that the presence of the atypical form of this
enzyme does not give a uniform explanation of this troublesome phenomenon. Therefore, preoperative quantitative, or even qualitative, testing of the plasma cholinesterase activity would only reduce, but not completely eliminate, the unexpected development of prolonged apnea after clinically used doses of suxamethonium.

The procedure of testing used in this investigation differed in certain aspects from those employed by Kalow and his associates, 15-17. Thus, instead of serum, heparinized plasma was the source of plasma cholinesterase in our studies. The spectrophotometric determinations were carried out at 37 C, instead of room temperature, the composition of the phosphate buffer 18 was different from the one used by Kalow; 15 and all inhibitors used were preincubated with the enzyme for twenty minutes before the addition of the substrate. Despite this, the observations made on the interrelationship of atypical plasma cholinesterase with the various substrates and inhibitors used are in good agreement with the findings of Kalow and his associates. 15-17.

It seems that the use of procaine instead of benzoylcholine as the substrate offers certain advantages in the detection of atypical plasma cholinesterase. The hydrolysis of procaine can be followed in the ultraviolet spectrophotometer at 313 mp, wave length where interference from proteins is much less than at the 240 mp, wave length used for the determination of the hydrolysis of benzoylcholine. What is even more important, however, is that the ratio of the rates of hydrolysis of procaine by the normal and atypical enzymes is more markedly decreased than that of any of the other substrates tested. Davies et al. 17 found that this ratio for a series of choline esters varied from 0.222 for butyrylcholine to 0.500 for benzoylcholine. In the present investigation these ratios varied in men from 0.17 for acetylcholine to 0.42 for suxamethonium and in women from 0.31 for acetylcholine to 0.62 for suxamethonium. The corresponding ratios for men and women with procaine substrate were 0.08 and 0.22, respectively. It is of interest that in women, whose plasma cholinesterase activity is significantly lower than that of men, 15 the ratios of the hydrolysis rates of all substrates by the atypical and typical enzymes were consistently higher than in men (table 3). Of the 16 subjects with atypical plasma cholinesterase who had prolonged apnea, five, all men, did not hydrolyze procaine at all. The hydrolysis rates of all the other substrates, although markedly reduced, were always measurable in these subjects. In contrast, in patients with low plasma cholinesterase activity due to liver disease, there was no marked difference in the relative hydrolysis rates of acetylcholine (0.26), succinylcholine (0.22), and procaine (0.21). Thus a zero or very low hydrolysis rate of procaine should arouse the suspicion of the presence of atypical plasma cholinesterase. This suspicion should then be confirmed by inhibitor studies. As suggested by Kalow and Gunn, 15 instead of dibucaine, RO2-0083, which is a 120-fold weaker inhibitor of the atypical than of the normal enzyme, 16 might be used to greater advantage than dibucaine to differentiate between the two varieties of plasma cholinesterase. This assumption was, indeed, confirmed by our findings (table 4). Based on the very weak inhibitory effect of succinylcholine (table 3) and decamethonium 18 on the atypical esterase, either one of these readily obtainable substances may also be used, instead of dibucaine, as an inhibitor. Because of its chemical stability decamethonium, which has the relatively lowest inhibitory effect on the atypical enzyme of all substances studied, 18 may be the agent of choice for this purpose.

It should be pointed out that subjects with low plasma cholinesterase activity may also be more sensitive than normal individuals to ester-type local anesthetic agents. These com-
pounds are also hydrolyzed by plasma cholinesterase. 

II. Plasma cholinesterase activity is decreased, manifestations of systemic toxicity may follow the clinical use of relatively large amounts of hydrolyzable local anesthetic agents. A reaction of this type was observed after the epidural administration of 22 ml. of 3 per cent 2-chloroprocaine containing 1:200,000 epinephrine to a 29 year old woman undergoing surgery for the relief of intestinal obstruction in her sixth month of pregnancy. Subsequent examination showed the patient's plasma cholinesterase was markedly reduced but qualitatively normal. One month after the termination of pregnancy cholinesterase activity was normal.

In subjects with atypical plasma cholinesterase the hydrolysis rate of procaine was found to be decreased more markedly than in patients in whom the level of the qualitatively normal esterase was decreased by some pathological change (i.e., liver disease). The same also applies to other ester-type local anesthetic agents, e.g., 2-chloroprocaine hydrochloride (Nesacaine) or mepivacaine hydrochloride (Carbocaine). Consequently, every individual in whom the presence of atypical plasma cholinesterase has been detected should be warned against the dangers associated not only with the use of hydrolyzable relaxants, but also with that of large amounts of hydrolyzable local anesthetic agents.

It was demonstrated earlier and confirmed in the present study that atypical plasma cholinesterase is frequently encountered in the family members of patients who developed prolonged apnea after the use of succinylcholine because of the atypicality of this enzyme. Therefore, whenever the presence of atypical plasma cholinesterase is detected after an abnormal reaction to succinylcholine or concomitantly to an ester-type local anesthetic agent, every effort should be made to investigate the plasma cholinesterase activity of the family members. When this is not possible, they should be warned that the use of hydrolyzable muscle relaxants or local anesthetic agents may cause serious complications in them. The advisability of this is illustrated by the fact that of the sixteen patients in this study who had atypical plasma cholinesterase and who developed prolonged apnea after succinylcholine, patients 12 and 13 were brothers and 11 and 15 were sisters. Despite the fact that succinylcholine-induced prolonged apnea had been encountered in one of each pair of siblings, subsequently succinylcholine was administered to their brother or sister too. Both of these also developed prolonged apnea. Investigation of the family members would have prevented the development of this complication in their siblings.

In the majority of cases preliminary screening for atypical plasma cholinesterase would make possible the detection of those individuals in whom the use of hydrolyzable muscle relaxants or local anesthetic agents would be accompanied by untoward reactions. Even though such screening of all patients in whom the use of these compounds is contemplated may not be feasible, at least the family members of subjects in whom this hereditary abnormality had already been detected should be investigated.

**Summary**

1. The plasma cholinesterase activity of 20 patients who developed prolonged apnea after the intravenous administration of relatively small doses of succinylcholine was investigated.

2. The substrates used were acetylecholine, butyrylcholine, succinylcholine, benzylcholine and procaine. The inhibitors employed were: neostigmine, RO2-0683, dibucaine and succinylcholine.

3. Of the 20 patients, plasma cholinesterase activity was qualitatively and quantitatively within normal limits in four. This indicates that succinylcholine-induced prolonged apnea is frequently but not always associated with the presence of atypical plasma cholinesterase.

4. Of the 16 patients with atypical plasma cholinesterase, 12 were atypical homozygotes and four were heterozygotes.

5. The plasma samples of 24 relatives of six patients were also studied. Of these 12 were heterozygotes, nine were normal, and three atypical homozygotes.

6. The enzymatic hydrolysis rate of all substrates was markedly reduced in the atypical homozygotes and less markedly in the heterozygotes. The hydrolysis rate of pro-
caine was more reduced than those of the other substrates.

7. The effect of all inhibitors studied was less on the atypical than on the normal enzyme.

8. It is suggested that procaine substrate and R02-0683 or decamethonium inhibitors may be more suitable for the detection of atypical plasma cholinesterase than benzylcholine substrate and dibucaine inhibitor.

9. The administration of large amounts of hydrolyzable local anesthetic agents to subjects with atypical plasma cholinesterase may also cause severe systemic toxic reactions.

10. It is suggested that, to prevent untoward reactions, the plasma cholinesterase activity of the relatives of subjects known to have this hereditary abnormality should also be investigated.

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Anesthesiology's Fifth Annual Symposium
July-August 1963

This Symposium is devoted to a basic treatment of many of the endocrine problems that confront the anesthesiologist as well as the interrelation of anesthetics and endocrine processes.

To accomplish these ends 14 authorities have contributed articles on the physiology and pharmacology of thyroidal disorders, diabetes mellitus, hyperparathyroidism, iatrogenic adrenal cortical insufficiency, pheochromocytoma, hyperfunctioning states of the adrenal cortex, and the sequelae of hypophysectomy.

These authors also review the effects of anesthesia and operation on renal function, the endocrine response to stress, intermediary carbohydrate metabolism, and response of the microcirculation to circulating hormones; the management of hyper tension of endocrine origin, effect of reserpine on the cardiovascular response to anesthetics; and, the effects of drugs on neuromuscular transmission in the central nervous system.

The Symposium may be ordered from the
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