THE RELATION OF PLASMA CHOLINESTERASES TO RESPONSE TO CLINICAL DOSES OF SUCCINYLCHOLINE*

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MANY MUSCULAR RELAXANTS have been introduced during the past decade. Of all these relaxants, succinylcholine is the only drug with a fleeting action. This short duration of action has been ascribed to a rapid enzymatic destruction of succinylcholine in the body (1, 2).

The only enzyme which is known to destroy succinylcholine in man is plasma cholinesterase. There are several synonyms for plasma cholinesterase. The enzyme is also called serum cholinesterase, pseudo-cholinesterase, or non-specific cholinesterase. The enzyme is distinctly different from acetyl-cholinesterase (or true cholinesterase) (3), which destroys acetylcholine *in vivo* and which is essential for various functions of the nervous system (4). Plasma cholinesterase is secreted by the liver into the blood (5), but its purpose is unknown. Besides being present in plasma and serum, this esterase occurs in various tissues (6), for instance in pancreas (7) and in the white matter of the human brain (8). Plasma cholinesterase differs in its behaviour from species to species (9), and it does not occur in the plasma of all mammals (10).

We shall first consider the enzymatic destruction of succinylcholine *in vitro*. The enzymatic deactivation of succinylcholine is a hydrolysis and proceeds in two steps (11, 12). First, succinyldicholine is split into succinylmonocholine and choline. Succinylmonocholine is roughly one-twentieth as active in man as succinyldicholine (13, 14). In the second step, which is a separate reaction, succinylmonocholine is split into succinic acid and choline.

Either succinyldicholine or succinylmonocholine combines with the esterase, and during this combination choline is split off. The combining power between enzyme and drug (15) is, therefore, an important measure but it is sufficient at the moment to state that the apparent affinity[1] between succinyldicholine and plasma cholinesterase is twenty times greater than the apparent affinity between succinylmonocholine and the enzyme (16). This is one of the reasons why the reaction occurs in two steps Figuratively speaking, if the enzyme has a free choice between succinyldicholine and succinylmonocholine, it prefers succinyldicholine However, the enzyme does not always have a free choice.

The rate of the enzymatic reaction depends on the following three factors: first, the intrinsic speed, second, the concentration of succinylcholine, third, the concentration of the esterase. We have to consider these three factors one by one.

First, there is the intrinsic speed with which the enzyme can handle succinylcholine. This is expressed as a maximum rate of reaction and we state this as

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[1]I.e., the reciprocal of the Michaelis constant. The constants were reported (16) as 1.3×10^{-3} for succinyldicholine and 2.6×10^{-2} for succinylmonocholine

follows. A normal adult has about 3½ litres of plasma. If these 3½ litres have an average esterase activity, they are capable of hydrolysing either 120 mg. of succinyldicholine chloride per minute (17), or 60 mg. of succinylmonocholine chloride per minute. Thus, at maximum rates the first step of the reaction between plasma cholinesterase and succinylcholine is twice as fast as the second step (16).

Second, the concentrations of succinyldicholine (16, 17) and succinylmonocholine (16) influence the rate of reaction. The maximum speed of destruction of succinyldicholine is obtained only if the enzyme is saturated with succinyldicholine, that is, at high concentrations of succinyldicholine. If the concentration of succinyldicholine is low, the rate of reaction is slow. The more its concentration rises, the faster it is destroyed until at very high concentrations the maximum rate is reached. The same rule holds for succinylmonocholine.

One cannot make a general statement saying that the first step of the hydrolysis is faster than the second step. The ratio of reaction velocities depends on the concentrations of the two compounds. If the concentration of succinylmonocholine is very high and the concentration of succinyldicholine very low, then succinylmonocholine would be hydrolysed faster. Therefore, there must be concentrations where succinyldicholine and succinylmonocholine are hydrolysed at the same rate, when both are simultaneously exposed to the esterase. A calculation shows that the first and the second steps of the reaction must be equally fast if the concentration of succinylmonocholine exceeds forty times the concentration of succinyldicholine [2] Or vice versa, if they are hydrolysed at the same rate, the ratio of concentrations is always 1 to 40 regardless of the actual concentration of succinyldicholine. This is a key figure for our later deductions.

Third, the rate of reaction is influenced by the concentration of the enzyme, which is often called the plasma level of cholinesterase. The rate of reaction is proportional to the concentration of esterase (17); thus, doubling the esterase level causes the reaction to proceed twice as fast. It is important to notice that this rule also holds at low concentrations of succinylcholine when the reaction rate is slow.

The significance of these enzymological data can now be discussed. There is no reason to assume that the enzyme acts differently towards succinylcholine *in vivo* than it does *in vitro*. Thus the circulating plasma cholinesterase of the normal adult could destroy up to 120 mg. of succinylcholine chloride per minute. We can conclude that the plasma cholinesterase is an important factor for the deactivation of succinylcholine in the human body.

[2]The equation for competitive inhibition is frequently described in the enzymological literature (e g, F M Huennekens in *Technique of Organic Chemistry*, vol. VIII, edited by A Weissberger [New York Interscience Publishers Inc, 1953], Equation 41, p 572 and equation 65, p. 586). For our calculation this equation was first written treating succinyldicholine as the substrate and succinylmonocholine as the inhibitor Thus, the first equation describes the rate of hydrolysis of succinyldicholine The second equation was set up treating succinyldicholine as the inhibitor, and calculating the rate of hydrolysis of the substrate succinylmonocholine If both these rates of hydrolysis are equal, the first and second equations can be combined to form a third equation By inserting numerical values for the Michaelis constants and the maximum velocity into the third equation, the above mentioned ratio of concentrations was obtained.

One can never reach the concentration of succinyldicholine in the circulating blood that would saturate the esterase and cause a maximum reaction rate. The esterase would act at only half the maximum rate if 1 to 2 gm. of succinylcholine were in the circulating plasma, and, also, this concentration is far in excess of practical limits. It follows that only a fraction of the available esterase can be active at any given time. We do not yet know the blood level of succinylcholine after injection, owing to the chemical difficulties of such a determination. We are, therefore, not sure how fast the circulating plasma cholinesterase acts *in vivo*, and whether we must expect that other factors contribute to the destruction of succinylcholine, such as the liver esterase. It has been found, however, that hardly any succinylcholine appears in the urine (18).

Although only a fraction of the available plasma cholinesterase will be occupied at any given moment by succinylcholine *in vivo*, the size of this fraction is proportional to the esterase level. In other words, the esterase does not act at its full capacity whether its level is high or low.

If one gives a slow constant intravenous drip of succinylcholine over long periods of time, a certain degree of relaxation will be achieved and maintained as long as the drip lasts (19). That means, the drip brings the plasma concentration of succinyldicholine to such a level that the esterase acts at a rate whereby just as much is destroyed per minute as one puts into the system. If the rate of drip is increased, the blood level will be higher, which causes the esterase to act faster, and a new equilibrium will be established. In other words, the blood level adjusts itself so that input and destruction are balanced.

This equilibrium must be maintained also for succinylmonocholine. The concentration of succinylmonocholine shortly after the start of the drip is very low so that it is destroyed very slowly, its concentration builds up, and correspondingly the destruction of succinylmonocholine becomes faster. Ultimately it will reach a level of concentration where its rate of formation is just as fast as its rate of destruction; in other words, succinylmonocholine will be removed just as fast as succinyldicholine is injected and destroyed. If the plasma cholinesterase is the only deactivating force, it follows that at equilibrium the plasma concentration of succinylmonocholine must be forty times as high as the concentration of succinyldicholine. Thus, from our present knowledge of the interaction between plasma cholinesterase and succinylcholine, we must predict that during slow intravenous infusion succinylmonocholine regularly accumulates.

When sufficient succinyldicholine was administered to achieve relaxation of momentary duration, succinylmonocholine could not possibly reach an effective level. Between these two extremes of rapid injection and prolonged drip, all intermediate stages of accumulation of succinylmonocholine must be expected to occur.

No matter how effectively the plasma cholinesterase can attack succinylcholine in the blood, the drug in the body is not always exposed to the esterase. Very shortly after intravenous injection, a major portion of succinylcholine must have left the blood vessels to be distributed over the extracellular space. Figure 1 explains this conclusion. It shows a schematic cross-section of single muscle fibres and capillaries in between. A motor nerve with its end-plate is shown

supplying one of the muscle fibres. After intravenous injection, the drug is carried by the blood into the capillaries. In order to reach the end-plate, the site of action of succinylcholine, the drug has to leave the capillaries and it must diffuse through the extracellular space. As is known from the rapid onset of action of succinylcholine, these processes of crossing the capillary walls and travelling through the extracellular space towards the end-plate must occur with great speed. The main driving force for these processes is probably the concentration gradient. The extracellular space outside the blood vessels is roughly three times as large as the blood volume. Thus, within a short time there must be more succinylcholine outside the blood than inside.

It is not very likely that the normal extracellular fluid contains much plasma cholinesterase. Ascitic fluid (20) and cerebrospinal fluid (21) have been shown

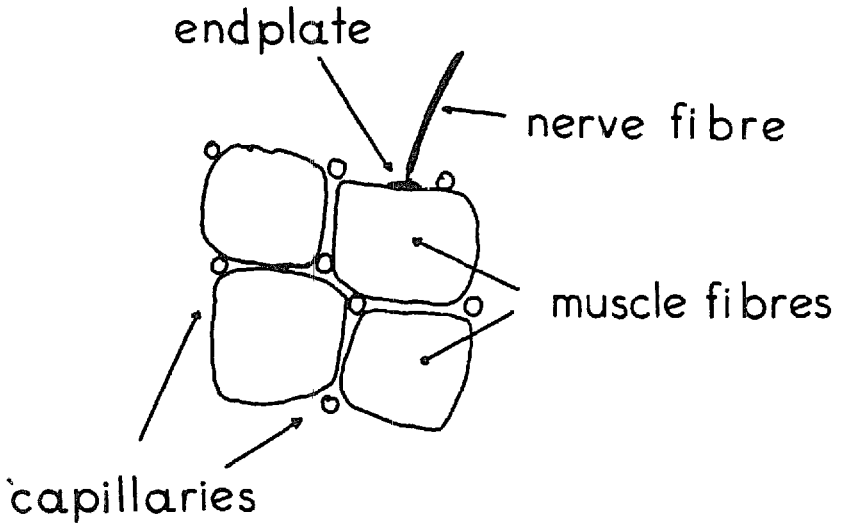

FIGURE 1. Schematic cross-section through single muscle fibres and capillaries. This figure demonstrates that a drug must leave the vascular bed and enter the extracellular fluid before it can reach the end-plate. Since the extravascular space is larger than the vascular bed, the drug becomes diluted and more of it must be outside the capillaries than inside. The figure was drawn after consultation with Dr. S. Bensley of the Department of Anatomy, University of Toronto.

to contain some, but very little, esterase. Thus, shortly after intravenous injection, a considerable portion of succinylcholine is in the extracellular space and thereby out of reach of the circulating esterase. In other words, the esterase guards the entrance to and the exit from the tissues but the esterase cannot be blamed for irregularities which might occur in the tissues, at the site of action of succinylcholine.

The foregoing theoretical deductions fit the following clinical experiences. First, the importance of the enzyme for the deactivation of succinylcholine has been confirmed by several observations. There are numerous reports of cases with a low esterase level where a prolonged apnoea after succinylcholine occurred (2, 22, 23, 24, 25, 26, 27, 28).

We can add here the description of some particularly instructive cases which were observed in Toronto. We had the opportunity to study three sera with

extremely low esterase activity from patients who had reacted with prolonged apnoea after succinylcholine.

On repeated routine investigations these sera showed an esterase activity between 30 and 50 units; the average plasma contains 210 units. To our surprise, these esterases showed some unusual behaviour in addition to their low activity. (Figure 2 gives an example.) The activity was not equally reduced towards

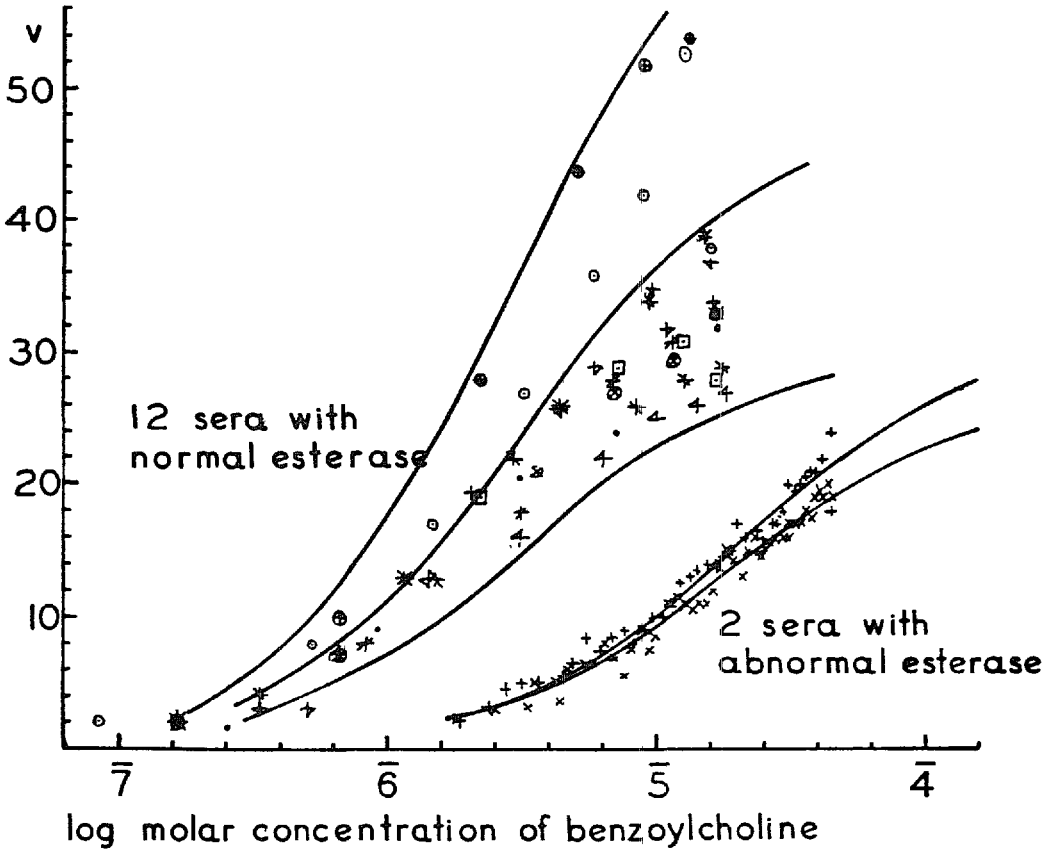

FIGURE 2. A contrast between normal and abnormal behaviour of human plasmacholinesterase. The rate of hydrolysis of benzoylcholine (determined by ultraviolet spectrophotometry) is plotted against log concentration of benzoylcholine. Experiments on different sera are designated by different symbols. The common type of variation between different sera causes the S-shaped curves to be more or less steep. The two abnormal curves are shifted horizontally. The abnormality has persisted for more than a year and is not confined to benzoylcholine. The hydrolysis of succinylcholine is not measurable. The presence of an unknown competitive inhibitor is excluded by dialyzing experiments.

various cholinesters, affinities were lower, and they were not so easily inhibited (for instance, by neostigmine). There were no signs of an unknown inhibitor. In short, there were changes which are hard to explain at the moment and which indicated a deeply distorted as well as a low esterase activity. Direct measurements revealed that these esterases split succinylcholine so slowly that no accurate data were obtained.[3]

One of these patients was anaesthetized by Dr. MacKay at the Toronto General Hospital. The patient was 6 feet tall, weighed 180 pounds, and was in good

[3]The enzymatic hydrolysis in the Warburg apparatus was considerably slower than the spontaneous hydrolysis of succinylcholine.

health except for a minor surgical condition. He was totally apnoeic for almost three-quarters of an hour after the injection of 40 mg. of succinylcholine iodide. Consciousness returned before respiration. Two sera were from mental patients of Dr. Gunn from the Ontario Hospital, New Toronto. They were given succinylcholine repeatedly for electroshock treatment and Dr. Gunn used these occasions to determine the optimal dose. One of these patients required only 5 mg. of succinylcholine chloride for adequate relaxation but the apnoea lasted for 8 to 15 minutes. Ten mg. caused apnoea for 22 to 25 minutes. The second patient required 10 mg. and the duration of apnoea was similar to that of the other patient, namely between 20 and 24 minutes. In these cases with extremely low esterase activity, succinylcholine acted almost as decamethonium acts in a normal person.

There are other types of evidence which demonstrate the importance of plasma cholinesterase for the metabolism of succinylcholine. The time of apnoea can be shortened by intravenous injection of purified plasma cholinesterase (28, 29, 30). The above holds, if the esterase is injected prior to the administration of succinylcholine (28). If the esterase is injected after the administration of succinylcholine, it does not terminate an existing apnoea (28). Under these circumstances, the injected esterase comes too late to guard the entrance into the tissues. Therefore, one cannot expect its full effect.

The injection of anti-cholinesterases, such as neostigmine, was repeatedly shown to increase the duration of action of succinylcholine (31, 32, 33, 34). Evans and co-workers (2) showed a close correlation between esterase level and duration of apnoea Foldes and co-workers (35) found a partial correlation. Among the mental patients in the Ontario Hospital, Dr. Gunn finds no correlation between esterase level and duration of apnoea, if the few exceptional cases which were reported above are disregarded. Since there is also no correlation between dose of succinylcholine and duration of apnoea, one suspects that the electroshock itself can modify the duration of action of succinylcholine to a certain extent.

A second theoretical conclusion was that the esterase in the body is not acting at its maximum capacity; in other words, that there is a reserve of esterase activity which can be utilized if the plasma concentration of succinylcholine is very high. This is confirmed by some experiments of Dr. Gunn who, on several occasions, administered 1000 mg. of succinylcholine chloride by rapid intravenous injection. The apnoea lasted for only a few minutes even after this extremely high dose. The esterase activity in these patients was normal. Similar observations were made by Borders and his co-workers (28) during anaesthesia.

Third, it has been presented as a theoretical deduction that succinylmonocholine accumulates regularly during continuous infusions of succinyldicholine. The significance of this conclusion cannot be evaluated for several reasons. It is not known whether there are more effective means than the plasma cholinesterase for the detoxification of succinylmonocholine. Such factors could prevent the accumulation which the esterase would cause.

Although the esterase action permits a prediction of ratios of concentrations of the two succinylcholines, the absolute values of these concentrations are

unknown. Furthermore, it is not known what drop of the plasma levels is necessary to terminate the relaxant actions. Thus, one cannot calculate how long the effects will persist after the termination of a continuous infusion or intravenous injection.

It is known that roughly twenty times more succinylmonocholine than succinyldicholine is necessary to produce a desired clinical effect. In view of the possible accumulation of succinylmonocholine, however, the potency of succinylmonocholine relative to that of succinyldicholine at the human motor end-plate may be less than it appears to be from a study of intravenous injections.

Finally, we concluded that one cannot expect that all unusual reactions with succinylcholine are due to a low activity of plasma cholinesterase. During the past year, we have received several samples of normal plasma from patients with prolonged apnoea after succinylcholine. Prolonged apnoea has been reported after all muscular relaxants (36), and some factor may occasionally affect the action of succinylcholine which could also affect some other relaxant.

Summary

The plasma cholinesterase of a normal adult is capable of destroying *in vitro* up to 120 mg. per minute of succinylcholine chloride. This great speed of destruction cannot be obtained *in vivo*, yet the normal plasma cholinesterase can effectively cope with a considerable excess of succinylcholine.

The rate of destruction of succinylcholine for any given concentration of succinylcholine is proportional to the concentration of plasma cholinesterase.

On slow intravenous infusion of succinyldicholine, the plasma cholinesterase must be assumed always to cause an accumulation of succinylmonocholine so that the concentration of succinylmonocholine exceeds by about 40 times the concentration of succinyldicholine. It is not yet clear whether this accumulation of succinylmonocholine is prevented by factors other than plasma cholinesterase, or whether this accumulation escapes clinical detection.

In order to exert its action at the neuromuscular junction, succinylcholine must enter the extravascular space where it is not exposed to plasma cholinesterase. Thus one cannot expect the esterase to be responsible for all abnormal reactions towards succinylcholine.

The sera of three patients are described, in these cholinesterase activity towards succinylcholine is too low to be measured. In all three cases the esterase has some peculiarities which are not fully explained. In one of these patients injection of 5 mg. of succinylcholine chloride was found to cause profound relaxation and 15 minutes' apnoea.

Acknowledgments

I wish to take advantage of this occasion to say some words of thanks. Without stimulus from Professor J. K. W. Ferguson and Dr. R. A. Gordon this paper would not have been written. Dr. Gordon continued his help by sending samples of plasma and discussing his cases. Dr. F. F. Foldes of Pittsburgh assisted by sending his data when our supply of succinylmonocholine failed. All calculations involving succinylmonocholine are based on unpublished data by Dr. Foldes.

Résumé

La plasma cholinestérase d'un adulte normal peut détruire *in vitro* jusqu'à 120 mg. per minute de chlorure de succinylcholine. *In vivo*, la réaction enzymatique n'est pas si rapide parce que la concentration plasmatique de la succinylcholine n'est pas assez élevée pour saturer l'enzyme. En d'autres mots, la plasma cholinestérase normale peut détruire plus de succinylcholine en peu de temps qu'il n'est nécessaire pour obtenir un effet de relâchement musculaire.

Pour une concentration donnée de succinylcholine, la vitesse de destruction doit être proportionnel au niveau plasmatique de la cholinestérase même si l'estérase n'agit pas à sa capacité maximum.

Lorsqu'une solution de succinyldicholine est injectée lentement en intraveineuse, on doit toujours se rappeler que la plasma cholinestérase cause une accumulation de succinylmonocholine de sorte que la concentration de succinylmonocholine est environ 40 fois celle de la succinyldicholine. On ne connait pas encore si cette accumulation de succinylmonocholine est arrêtée par d'autres facteurs que la plasma cholinestérase ou bien si elle échappe à l'investigation clinique.

La succinylcholine agit à la jonction neuro-musculaire. Pour l'atteindre, la succinylcholine doit entrer dans le milieu extra cellulaire. Dans le liquide extravasculaire la succinylcholine n'est pas au contact de la plasma cholinestérase. En d'autres mots, l'estérase previent l'entrée et la sorties dans les tissus mais ne peut être tenu responsable des irrégularités qui peuvent survenir dans les tissus au lieu d'action de la succinylcholine

Il est connu que la concentration de plasma cholinestérase varie d'une personne à une autre. Habituellement il s'agit et une variation de quantité de l'enzyme mais il peut survenir aussi des variations dans les propriétés de la plasma cholinestérase. Seulement dans trois de ces cas, l'activité de l'estérase sur la succinylcholine fût trop basse pour être mesurer. Chez l'un de ces patients, l'injection de 5 mg. de succinylcholine causa un relâchement musculaire profond et une apnée de 15 minutes.

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