PLASMA CHOLINESTERASE STUDIES IN SOME PATHOLOGICAL CONDITIONS IN MAN

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IN the last few years, there has been a growing interest in plasma cholinesterase. Until recently, study of this subject has been mostly confined to physiological and biochemical laboratories. The discovery of organic phosphorous ester-type war gases, the introduction of anti-cholinesterase substances, such as insecticides in agriculture, and the recent use of succinylcholine as a relaxant in anaesthesia—all these events have made the knowledge of cholinesterase properties of very practical value (1, 2).

Cholinesterases are enzymes widely distributed in animal tissues. They catalyse the hydrolysis of acetylcholine. Two types of this enzyme have been described and can be identified by chemical tests (3, 4): the specific cholinesterase of tissues and red cells, and the non-specific cholinesterase in the plasma also called pseudo-cholinesterase.

There is now little doubt as to the physiological role of the specific acetylcholinesterase which is bound to the cell membranes, its function seems to be ultra-rapid inactivation of free acetylcholine. This reaction is essential for the development and propagation of the action potential and for the metabolism of all nerve cells (5). The importance of this enzyme for normal life has been demonstrated clearly by the fact that selective inhibition of its activity by organic phosphorous ester-type war gases is very rapidly fatal to man and other animals.

On the other hand, there is practically nothing known about the physiological role of the non-specific cholinesterase which is present mainly in the plasma. No substrate has been found equivalent to acetylcholine which would explain the presence in plasma of this highly active and potent esterase. Selective poisoning of plasma cholinesterase by D.F.P. (di-isopropyl fluoro-phosphate) injections in experimental animals and in man has not been fatal even when the enzyme activity was reduced to zero (18). This is in sharp contrast to the effect of complete inactivation of true cholinesterase, which is rapidly fatal.

In spite of the apparent lack of importance and the surrounding mystery of its function, we have been interested in plasma cholinesterase because it has been demonstrated to hydrolyse succinylcholine *in vitro* and *in vivo* (2). Studies of the behaviour of cholinesterase in the plasma might be of some use to us if we have to depend on its activity in our daily anaesthetic practice (6, 7).

METHODS OF ESTIMATING CHOLINESTERASE

All chemical methods depend upon measurement of the acid produced by the action of cholinesterase on acetylcholine. We have been using the electrometric method of Michel (12). The drop in pH resulting from the liberation of acetic acid, when acetylcholine is hydrolysed, is measured with a glass electrode at

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25°C. The result is then corrected for non-enzymatic hydrolysis by the use of Michel's tables and the plasma cholinesterase activity is expressed in units of decrease of pH per hour ($\Delta\text{pH}/\text{hour}$). Other methods used to estimate esterase level are: titrimetric technique of Willstatter *et al.* (8); gasometric method of Ammon (9) or McArdle (19); photometric method of Croxatto (10); colorimetric method of Ravin (11); biological estimations of Hicks and MacKay (20).

NORMAL VALUES OF CHOLINESTERASE ACTIVITY

Callaway *et al.* (15) determined cholinesterase in 247 healthy adults in England and found the plasma cholinesterase to be between 57 and 143 per cent of the mean value. They found no sex, age, or seasonal differences.

Vorhaus and Kark (14) in 120 healthy individuals found a normal range for serum cholinesterase to be from 0.62 to 1.26 units. They found no correlation between the enzyme activity and age, sex, weight, height, or surface area. There were neither diurnal nor seasonal fluctuations.

In spite of a wide range of normal values, all investigators confirmed that individuals have a very constant normal level which does not vary in health. For that reason, interpretation of single measurements may often be difficult, but repeated tests have been found of great service to follow the degree of recovery from organo-phosphorous poisoning (22).

DEVIATIONS FROM NORMAL PLASMA CHOLINESTERASE VALUES

Several investigators attempted to correlate plasma cholinesterase activity with various pathological conditions. The most constant finding was a reduction of cholinesterase in liver disease (17) and an increase in nephrosis (14). A close correlation exists between plasma levels of albumin and cholinesterase (23). The lower cholinesterase activity in liver diseases is probably due to impaired hepatic synthesis of this substance and, for that reason, cholinesterase estimations were recommended as a very sensitive liver function test (24, 21, 14).

Our main interest has been to try and estimate to what extent cholinesterase activity is reduced in liver disease and how patients with hepatic pathology react to succinylcholine infusion.

The investigations of Vorhaus and Kark (14) demonstrated that patients with obstructive jaundice have an enzyme activity within normal limits, those with acute hepatic conditions such as virus hepatitis or ascending cholangitis have moderately depressed cholinesterase, and those with chronic liver diseases with marked hepatic tissue damage, such as occurs in cirrhosis, have the lowest cholinesterase values.

CASE HISTORIES

Our diagram shows the cases of five patients with low cholinesterase activity who made an uneventful recovery from succinylcholine continuous infusion during the operation.

Case No. 1. A man, 42 years of age, 150 pounds, diagnosed as having advanced cirrhosis of the liver. Plasma cholinesterase had been estimated preoperatively and found to be within the lower range of normal values, 0.66 units. Liver biopsy was

FIGURE 1. Deviations from normal plasma cholinesterase activity in various clinical circumstances.

performed under general anaesthesia with thiopentone, nitrous oxide, oxygen and an infusion of succinylcholine 0.15 per cent. A total of 150 mgm. of this relaxant were used during the surgical procedure which lasted one hour. On extubation, the patient showed complete recovery of muscular power,

Case No. 2. A 40-year-old female, 120 pounds, with obstructive jaundice, was found to have cholinesterase activity of 0.36 units. During a three-hour operation under nitrous oxide and oxygen anaesthesia, she received 150 mgm. of succinylcholine at a rate of 0.8 mgm. per minute, with normal recovery from the effects of this relaxant. Biopsy of the liver confirmed the diagnosis of advanced cirrhosis.

Case No. 3. A man, 35 years old, 135 pounds, with advanced cirrhosis of the liver and a cholinesterase activity of 0.34 units, had a liver biopsy performed under general anaesthesia. Over a period of 45 minutes, a total of 100 mgm. of succinylcholine were used as an adjuvant to thiopentone and nitrous oxide anaesthesia, at a rate of 2.2 mgm. per minute. Recovery was prompt and uneventful.

Case No. 4. This man, 44 years of age, 122 pounds, with suspected advanced homologous serum hepatitis, had an exploration of the common bile duct under general anaesthesia, his serum cholinesterase being at the level of 0.60 units. During a three and a half hour operation, 500 mgm. of succinylcholine were used with nitrous oxide and oxygen anaesthesia. A month later, one day prior to his death from hepatic failure, his plasma cholinesterase activity was still at the level of 0.26 units.

Case No. 5. Terminal liver failure in a 55-year-old man, 165 pounds, necessitated a laparotomy of 40 minutes' duration. With a cholinesterase activity of 0.20 units, he received, during the whole procedure, 50 mgm. of succinylcholine, recovery from anaesthesia being uneventful.

The above cases led us to believe that, even in advanced hepatic failure, continuous succinylcholine infusion may be used for obtaining relaxation in anaesthesia, provided due care is exercised to avoid an overdose. In contrast with the above-mentioned five cases, we had three cases of prolonged apnoea following the use of succinylcholine although, as shown on the diagram, all of them had cholinesterase values within normal limits.

PATIENTS WITH PROLONGED APNOEA

Patient	Dose of succinylcholine	Cholinesterase (units)	Duration of apnoea	Remarks
A. Age 29	60 mgm.	0.86	40 min	Technical difficulties with controlled respiration
B. Age 48	40 mgm	0.80	60 min	Deficient CO ₂ elimination
C. Age 51	40 mgm	0.63	60 min	Deficient CO ₂ elimination

Low plasma cholinesterase might be a contributing factor in some instances of prolonged apnoea, but our limited number of cases appeared to fall into the group where carbon dioxide retention could be suspected as the main factor producing symptoms of curarization as described by Scurr (25) and others (26, 27, 34). Gesell and Hansen (28) have demonstrated that carbon dioxide decreases the rate of destruction of acetylcholine by cholinesterase, but it is not yet known if this anti-cholinesterase action of carbon dioxide is strong enough to be of clinical significance in man.

EFFECT OF ORGANO-PHOSPHORUS INSECTICIDES ON PLASMA CHOLINESTERASE

Warnings against the use of succinylcholine in cases where there is history of exposure to this type of pesticides have been issued. Barnes and Davies (22) found reduced cholinesterase levels only in twelve workers out of eighty exposed to this type of chemical. Plasma cholinesterase level was found to be between 44 and 49 units, just below the normal values of 51 to 127 units according to their method. We had only one patient with a history of recent exposure to this type of insecticides and his preoperative cholinesterase level was 0.42 units. During a two-hour operation for cholecystectomy, he received 150 mgm. of succinylcholine, with a prompt and uneventful recovery.

CAUSES OF DEPRESSION OF PLASMA CHOLINESTERASE

Burnett and Cohen (24) reported a reduced plasma cholinesterase activity following operative procedures, which was most marked on the fifth postoperative day. As shown on our diagram, this reduction appears to be small, but in cases where the preoperative level is already low, it may become an additional factor tending towards cholinesterase insufficiency if and when a second operation has to be performed within a few days following the first one.

Malnutrition. Milhorat (42) has found very low values in patients with extreme cachexia and debilitation. The esterase activity in this type of patient was one-

fifth to one-tenth of normal. Such a low range is equivalent to that found in extreme cases of hepatic failure.

Prolonged fasting was found to be without effect on cholinesterase (42).

Reduced cholinesterase activity has been reported in cases of *schizophrenia*, *epilepsy*, and *catatonis stupor* (31). For schizophrenics, our estimations were within the lower range of normal values.

Acute infectious diseases have been reported to depress cholinesterase only to a slight extent. (14).

Anaemias. In various types of anaemias, a reduced esterase activity has been reported (29), although the reduction is not as great as in hepatic failure. The lowest readings were found in pernicious anaemia, in relapse and in acute leukaemia.

Therapeutic irradiation and radiation sickness (30). This type of condition has been reported to produce a drop in cholinesterase; the report should be kept in mind if one has to anaesthetize patients who have been given preoperative deep X-ray therapy.

EFFECT OF DRUGS

The reversible depression of cholinesterase activity by *physostigmine* and *prostigmine* is well known. A permanent inhibition of the enzyme is effected by the *alkyl-fluoro-phosphates* which are used as insecticides (e.g., D.F.P.).

Most *anti-malarial drugs* are very effective inhibitors of plasma cholinesterase: paludrine, plasmoquin, quinidine and quinine are included in this group (32).

Intensive treatment with *Vitamin K analogues*, often started before operation, may slightly depress cholinesterase (33). In our cases, the drop was never more than 0.10 to 0.15 units.

Similar effect is obtained in some patients receiving *Vitamin B-1—Thiamin* (35) in preoperative intravenous infusions. The reduction of activity in our cases was up to 0.20 units. However the increase in plasma volume produced by intravenous administration of fluids with a vitamin B-1 content may be partly responsible for the drop in enzyme activity.

Atropine and *Scopolamine* (36), morphine and its derivatives (37), chloroform and ether (38), barbiturates (5), curare (5), and cyclopropane in clinical dosage, have no significant influence on cholinesterase (16, 39).

On the other hand, substances which have been found to increase cholinesterase activity include *folic acid* (40) and *Vitamin E* (41).

SUMMARY AND CONCLUSIONS

A review of pathological conditions and of specific drugs which may affect plasma cholinesterase in man has been made. Short of experimental D.F.P. injections, there appear to be very few instances where reduction of plasma cholinesterase would bring it to such low values as to become a contra-indication to the use of succinylcholine. However, cases of severe hepatic damage and cachectic states exhibit the lowest plasma cholinesterase levels and, for that reason, it would seem advisable to exercise extreme care in the use of this relaxant.

Three cases of prolonged apnoea following infusion of succinylcholine have been reported, none of them exhibiting any deviation from normal plasma cholinesterase levels.

RÉSUMÉ

Les auteurs font allusion au rôle de la cholinestérase cellulaire par contraste avec la cholinestérase plasmatique ou pseudo-cholinestérase. Pour l'estimation de cette dernière, ils ont fait appel, entre autres, à la méthode électrométrique de Michel, basée sur la diminution de pH résultant de l'acide acétique libéré à l'occasion de l'hydrolyse de l'acétylcholine par la pseudo-cholinestérase.

Les valeurs normales, basées sur cette méthode, se chiffrent de 0.62 à 1.26 unités.

Les estimés ont été faits en vue d'apprécier d'une part le rôle joué par la pseudo-cholinestérase dans l'hydrolyse de la succinylcholine employée comme adjuvant en anesthésie, et de déterminer d'autre part l'influence que peuvent exercer certains états pathologiques ou certains agents chimiques et médicamenteux sur le taux de pseudo-cholinestérase et, indirectement, sur l'intensité d'action de la succinylcholine aux doses cliniquement employées.

Le niveau de la pseudo-cholinestérase a été trouvé abaissé dans certains états pathologiques tels que l'insuffisance hépatique, l'empoisonnement par insecticides, la malnutrition, l'état post-opératoire, la schizophrénie, les anémies, etc. . . —et à la suite de l'emploi de substances médicamenteuses telles que prostigmine et physostigmine, vitamine B-1, etc. . .

Les états s'accompagnant d'une baisse de pseudo-cholinestérase offrent-ils une sensibilité plus marquée à l'action de la succinylcholine? De l'opinion des auteurs, cette sensibilité, bien que présente, ne fera pas la règle et une curarisation prolongée secondaire à l'emploi de succinylcholine serait plus spécifiquement imputable à une rétention de gaz carbonique. Un taux bas de pseudo-cholinestérase n'exclut donc pas l'emploi de succinylcholine, mais engage simplement à une plus grande prudence.

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