RELATIONSHIP BETWEEN SUXAMETHONIUM APNOEA, SERUM CHOLINESTERASE ACTIVITY AND INHIBITOR NUMBERS

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SUMMARY

Two of the factors contributing to the lack of correlation between biochemical parameters and the sensitivity of patients to suxamethonium are shown to result from the reaction temperature employed in the analytical procedure. It is also shown that this cannot be remedied without losing the ability to categorize precisely the cholinesterase phenotype.

Numerous methods are available for the estimation of serum cholinesterase (Hunter, 1970; Augustinson, 1971) and there is an increasing literature on means of identifying the phenotype of the cholinesterase variants. However, despite the newer approaches, following a suxamethonium apnoea, the accepted standard assay is that of Kalow and Lindsay (1955). Also despite the proposed use of other inhibitors, n-butyl alcohol (Whittaker, 1968a), chloride (Whittaker, 1968b), formaldehyde (Whittaker, 1969), urea (Hånel and Mogensen, 1971), or succinylidicholine (King and Griffin, 1973), determination of the dibucaine number (Kalow and Genest, 1957) and fluoride number (Harris and Whittaker, 1961) still remain the most precise indices of cholinesterase phenotype. Recently published information on inhibitor numbers (King and Griffin, 1973), is summarized in figure 1 and constitutes the phenotype “guessing chart” in these laboratories. Of the six phenotypes shown, the E1, E1, E1, E1, E1, and E1, and of course the silent gene homozygote E1, E1, who is devoid of serum cholinesterase, are invariably sensitive to suxamethonium and exhibit a prolonged paralysis after its administration.

“One man’s meat . . .”

To every request for laboratory assistance there are two facets, that of quickly, simply and accurately carrying out the test, which is the concern of the biochemist, and that of the interpretation of the result which is the problem of the anaesthetist. Hunter (1970) has already pointed out the confusion which results when a variety of tests are used each being reported in different units, with different ranges of normal values. The problem is only exacerbated by many of the newer approaches and procedures which seem designed for ease and speed of biochemical manipulation.

This is not always the case though, for the standard method of cholinesterase phenotyping employs a benzoylcholine substrate, the hydrolysis of which is monitored at 240 nm. This requires a sophisticated ultraviolet spectrophotometer and the procedure which is time-consuming demands more than the usual technical ability. Despite these obvious handicaps most biochemists would still advocate this procedure because it is the best method currently available for phenotyping serum cholinesterase. This is the standpoint of the laboratory worker and there could be little dissatisfaction with it, were the results as definitively able to be interpreted by the anaesthetist; that is, did the level of cholinesterase activity and inhibitor numbers correlate with the sensitivity of the patient. However, Telfer, McDonald and Dinwoodie (1964) and Lehmann and Liddell (1969) have indicated that 50% of patients suffering from suxamethonium apnoea are the usual homozygotes or heterozygotes. In the present state of our knowledge these cases cannot be predicted and may not always be the result of inherited abnormalities, as anaesthetists readily appreciate. Nonetheless, where a sensitivity is predictable by biochemical criteria it would seem reasonable to expect that the lower the cholinesterase activity and the lower the dibucaine and fluoride numbers the longer would be the apnoeic response to suxamethonium. In general this is certainly so, but not always and in those cases the explanation lies in the biochemical techniques employed.
Figures 2 and 3 illustrate a series of estimations carried out at 25°C and 37°C respectively using the assay of Kalow and Lindsay (1955). The usual homozygote group illustrated in these figures is by no means representative of a normal population and contains at least six, presumptive but almost certain, usual/silent heterozygotes E₁₉ E₁₁. Also included are a number of hospital patients, some suffering from diseases in which low cholinesterase concentrations are to be expected. Despite this, it is readily seen that there is a wide overlap of activities from all phenotypes at 25°C (fig. 2) and that a number of suxamethonium-sensitive individuals have serum cholinesterase activities which can only be classed as normal. The distribution of activities for the usual homozygotes is relatively unchanged at 37°C. The activity of the three suxamethonium-sensitive phenotypes is, however, markedly reduced and all these activities now become abnormally low (fig. 3). These findings corroborate earlier work (King and Dixon, 1969; King and Morgan, 1970) which indicated that a valid assay of cholinesterase activity was only obtained at 37°C.

Inhibitor numbers.

The second absence of correlation between enzymic parameters and apnoeic response occurs with the fluoride-resistant homozygote, E₁₁ E₁₁, which is seen (fig. 1) to have a dibucaine number, and chloride and Scoline numbers also, of the same order as the non-sensitive usual/atypical heterozygotes.
zygote E₁ E₁. Again the explanation lies with the assay temperature used and figure 4, which combines the data of King and Dixon (1970) and King, McQueen and Morgan (1971), shows that the dibucaine inhibition response to temperature of the E₁ E₁ phenotype is more pronounced than the others. At 37°C, the temperature at which the patient exhibits the sensitivity, the dibucaine number is similar to that of the predictably sensitive E₁ E₁ phenotype.

In view of these facts it would seem desirable for all concerned to conduct the biochemical investigations at 37°C. Then the tests would be more quickly carried out, technical difficulties in maintaining a constant temperature would be alleviated and the results would be more readily understood. The exception to this is illustrated in figure 5 which shows that fluoride inhibition is acutely temperature dependent. It is possible by manipulation of substrate and inhibitor concentra-

![Distribution of cholinesterase activities by phenotype at 37°C](image1)

**Fig. 3.** Distribution of cholinesterase activities by phenotype at 37°C. The vertical broken line indicates the lower limit of normal.

![Variation of dibucaine numbers with reaction temperature](image2)

**Fig. 4.** Variation of dibucaine numbers with reaction temperature.

![Variation of fluoride numbers with reaction temperature](image3)

**Fig. 5.** Variation of fluoride numbers with reaction temperature.
tions to retain the phenotype discrimination of dibucaine. However, even with substrates other than benzoylcholine it has not proved possible to do so with fluoride inhibition at 37°C. As can be readily appreciated from figure 1 it requires two inhibitor numbers, one of which must be fluoride, to provide a precise phenotype identification and this must be at the lower temperatures currently employed. Perhaps, however, an understanding of the two effects of temperature considered above will permit a better correlation between the biochemical specifications and the anaesthetic realities.

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REFERENCES


