ANALYSIS OF SUXAMETHONIUM SENSITIVITY FOLLOWING TERMINATION OF PREGNANCY

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One of the physiological factors associated with pregnancy is a significant decrease (about 20%) in plasma cholinesterase activity (Piccoli and Longo, 1947; Robertson, 1966). Although some ambiguity has arisen about the pattern of change in the enzymic activity during pregnancy, it is now accepted that a rapid decrease in cholinesterase activity occurs during the first trimester of pregnancy (Levine and Hoyt, 1949; Evans and Wroe, 1980). The decrease in activity is sustained until delivery.

Plasma cholinesterase variants have decreased enzymic activity relative to the usual homozygote E_{1}E_{1} (Whittaker, 1986). Heterozygotes in general are not sensitive to suxamethonium, but a rather longer period of muscle paralysis, of not more than 10 min (compared with about 2–4 min for the usual homozygote) is observed. Indeed, some anaesthetists can predict a heterozygote from observation of the duration of paralysis following the administration of a standard dose of suxamethonium to their patients (Vickers, personal communication). It is, therefore, desirable to ascertain the effect of pregnancy on the duration of apnoea in heterozygotes following a standard dose of suxamethonium. Blood samples from patients showing sensitivity to suxamethonium following termination of pregnancy have been sent to Exeter for phenotyping of cholinesterase variants. These samples were the basis of this study.

MATERIALS AND METHODS

Thirty-five blood samples, from patients in the same Nursing Home, were phenotyped for cholinesterase variants during a 3-year period. All patients were reported to have experienced suxamethonium sensitivity following anaesthesia for the termination of pregnancy. The operative procedure was usually of about 5 min duration. This necessitated a brief anaesthetic which consisted of a barbiturate i.v. (usually methohexitone, but sometimes thiopentone) and intermittent positive pressure ventilation using nitrous oxide and oxygen. The trachea was not intubated. A small dose of suxamethonium (usually 20–25 mg or less) was used and, in consequence, the apnoea was very transient. Recovery of spontaneous respiration almost invariably occurred before the patient was ready to be lifted off the operating table. The definition of “scoline apnoea” in these patients was inadequate ventilation 2–3 min on the trolley after being lifted off the table. Thus the minimum period for an apnoea was approximately 10 min. A 10-ml heparinized blood sample was sent for phenotyping for all patients who experienced an apnoea of 10 min or longer. Cholinesterase activity was assayed by the method of Kalow and Lindsay (1955) and genotyped by measuring dibucaine, fluoride and RO2 numbers (Whittaker, 1986).

SUMMARY

The cholinesterase genotypes in the majority (25/35) of patients with suxamethonium sensitivity following termination of pregnancy are heterozygotes with an E_1^o gene. Twelve of these patients have the genotype E_1^E_1^o. The reported duration of apnoea is minimal in the heterozygotes lacking the E_1^o gene (about 5–10 min) and maximal in the homozygotes E_1^oE_1^o (about 35 min). With few exceptions, the heterozygotes having an E_1^o gene are apnoeic for 10–15 min. The apparent low frequency of suxamethonium in these patients is discussed.
RESULTS

The distribution of genotypes found in 35 suxamethonium-sensitive patients is given in table I. The range and mean duration of apnoea for each genotype are also included in the table.

DISCUSSION

It is apparent from the results given in table I that the individuals who experienced sensitivity to suxamethonium following the termination of pregnancy were not confined to the cholinesterase genotypes $E^aE^a$ and $E^aE^b$. In this study nearly 70% of the patients were heterozygotes having an $E^a$ gene. This closely matches our earlier observation that an increased frequency of suxamethonium sensitivity occurs in the heterozygotes $E^aE^b$ during pregnancy (Whittaker, 1980). At that time we did not differentiate between the heterozygotes $E^aE^b$, $E^aE^k$ or $E^aE^l$. A frequency of about 7% has been reported for the $E^aE^b$ heterozygote in suxamethonium-sensitive surveys of ECT patients (Owen and Hunter, 1983) and general surgical patients (Lehmann and Liddel, 1969; Viby-Mogensen and Hanel, 1978).

Analysis of the results of the present study has not differentiated between the genotypes $E^aE^a$ and $E^aE^b$—both types have been classified as $E^aE^a$. In this survey only nine patients (one $E^aE^a$ phenotype) have accepted family studies. Thus it is impossible, in the absence of family confirmation, to assign a silent gene as a true interpretation of a low enzymic activity when the condition of pregnancy produces such an effect. However, very few previous surveys of the distribution of phenotypes occurring in suxamethonium-sensitive individuals have segregated these two genotypes and 43.2% of 1346 sensitive individuals have the $E^aE^a$ phenotype (Whittaker, 1986). It is universally accepted that all individuals having this phenotype are sensitive to suxamethonium but, in the current study, we have found only 20% with this phenotype. The discrepancy may be explained by the size of sample or, more probably, by the large increase in frequencies of the heterozygotes $E^aE^b$ and $E^aE^k$ (50% compared with 10.5% from the 1346 individuals reported above).

An ancillary approach to the validity of the 20% atypical homozygotes in our survey can be assessed by comparing the theoretical and actual number of patients being anaesthetized in this hospital each year during the 3-year period of the study. The frequency of the $E^aE^b$ phenotype in a British population is approximately 1 in 1800. This frequency can be used to estimate the number of females presented for surgery in this Nursing Home during the 3 years of the survey as $7 \times 1800 = 12600$ or about 4200 per annum. The Records Department has supplied figures of 7967, 8401 and 8578 for the 3 years covered by the survey. An annual average of 8315 patients is at variance with our estimate. This apparently low incidence of suxamethonium sensitivity in our study could be partially explained by the use of other neuromuscular blocking drugs in some patients undergoing sterilization or, rarely, other surgery. All our patients showed suxamethonium sensitivity during the termination of their pregnancies. It is also possible that a proportion of patients who did show sensitivity to suxamethonium were not referred, for various reasons, for phenotyping of the cholinesterase variants.

Viby-Mogensen (1982) has studied the reaction of phenotypically different cholinesterase to suxamethonium using train-of-four nerve stimulation. He demonstrated that the existence of two abnormal genes, compared with only one, dramatically changes the response to the drug in so far as the duration of apnoea and the time for...
recovery of adequate ventilation, are significantly prolonged. Our records for the present survey confirm these observations for the E_{1}^{a}E_{1}^{a} phenotype, but no substantial prolongation of apnoea is apparent in either the E_{1}^{a}E_{1}^{f} or the E_{1}^{a}E_{1}^{k} genotypes. Our sample is small with only five and six of these heterozygotes, respectively.

Evidence for the ambiguity of sensitivity of the E_{1}^{u}E_{1}^{a} heterozygote also has been provided by Viby-Mogensen (1981). He showed that 50% of these heterozygotes experience a moderately prolonged response to suxamethonium and 10% of these individuals did not have normal neuromuscular transmission, as demonstrated by train-of-four nerve stimulation, for 20 min. At that time Viby-Mogensen (1981) did not differentiate between the heterozygotes E_{1}^{u}E_{1}^{a} and E_{1}^{a}E_{1}^{k}, but in the current study only the heterozygotes E_{1}^{u}E_{1}^{a} are reported to have an apnoea of 20–25 min. Our results support the observation of Viby-Mogensen (1981) that heterozygote patients will develop an apnoea more readily than the usual homozygote, E_{1}^{a}E_{1}^{u}.

We have found no correlation between the duration of apnoea and cholinesterase activity, but it is apparent from the results in table I that the duration of apnoea is very dependent on the genotype of the pregnant patient.

The vast majority of reports of suxamethonium-sensitive individuals have not used a nerve stimulator to demonstrate prolonged neuromuscular blockade and thus confirm the drug-induced apnoea. Some patients are over ventilated and apnoea as a result of hypocapnia can be misinterpreted as suxamethonium sensitivity. From a surgical population of 24945 pregnant patients seeking termination of pregnancy, 35 individuals have been found to be sensitive to suxamethonium. This low frequency of sensitivity provides scant evidence for the avoidance of the use of suxamethonium in women seeking termination of pregnancy.

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REFERENCES


