THE EFFECT OF TUBOCURARINE AND SUXAMETHONIUM ON DIRECTLY AND INDIRECTLY ELICITED CONTRACTIONS OF SKELETAL MUSCLE IN UNANAESTHETIZED MAN USING SINGLE AND TRAIN OF FOUR IMPULSES

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- 1 Contractions of adductor pollicis in unanaesthetized man were elicited by direct and indirect stimulation. Single twitch responses as well as those by a train of four impulses at 2 Hz for 2 s were elicited for indirect stimulation.
- 2 After a suitable control period, tubocurarine (0.05 mg/kg) or suxamethonium (0.08 mg/kg) was administered intravenously.
- 3 A stepwise diminution in the train of four impulses was noticed after tubocurarine. Indirectly elicited contractions due to single stimulus and direct muscle stimulation remained unaltered.
- 4 Partial blockade of transient duration occurred after suxamethonium for single as well as train of four stimuli. Directly elicited contractions remained unchanged. The intensity of blockade depended on the rate of injection of suxamethonium.
- 5 Indirectly elicited contractions by train of four impulses is a reliable and sensitive method for testing neuromuscular blocking drugs in unanaesthetized man.

Introduction

The effects of neuromuscular blocking drugs have been studied in man based on clinical observation of signs of muscle weakness (Mushin, Wien, Mason & Langston, 1949; Unna, Pelikan, Macfarlane, Cazort, Sadove & Nelson, 1950; Unna & Pelikan, 1951; Bodman, 1952). Measurement of voluntary contractions however is not very useful since individual effort is not always constant or reproducible. Stimulation of a suitable motor nerve and recording the evoked response appears to be the best method for studying the neuromuscular blocking drugs (Katz, 1965). Delivering a single stimulus or tetanic stimulation and recording the changes in the response has been used to measure the intensity and type of neuromuscular block. Thus, evoked responses have been used to detect nondepolarizing block (Churchill, Davidson & Christie, 1959; Epstein & Epstein, 1973; Katz, 1973; de Jong & Freund, 1967) depolarizing block (Churchill-Davidson & Christie, 1959; de Jong & Freund, 1967; Katz, 1973); and dual or phase II block (Crul, Long, Brunner & Coolen Joan, 1966; Churchill-Davidson, Christie & Wise,

1960). Since tetanic stimulation of a nerve is painful and virtually unacceptable to an unanaesthetized individual, Ali, Utting & Gray (1970), have proposed the use of a short train of four stimuli at a frequency of 2 Hz for 2 s. The technique is not painful and can be employed to study drugs acting at myoneural junction in unanaesthetized individuals. Tubocurarine has been studied in conscious volunteers (Ali, Wilson, Savarese & Kitz (1975); and in anaesthetized patients (Ali *et al.*, 1970). A large variation in the effects of tubocurarine was observed in their study in conscious volunteers. Suxamethonium, has been studied only in anaesthetized subjects (Ali *et al.*, 1970; Lee, 1975). No study on unanaesthetized volunteers has been reported using train of four stimuli and the effect of suxamethonium on it. The present study was undertaken to study the effect of suxamethonium on evoked responses using a train of four stimuli in conscious volunteers and to compare its effect with that of tubocurarine. Direct stimulation of the muscle was also done to study the effects of these drugs.

Methods

Eight healthy volunteers between 20 to 40 years of age were taken for the study. Informed consent was obtained. The subjects were reclined in a comfortable position. Stimulating electrodes were placed on the ulnar nerve proximal to its entry in the wrist joint. Another set of electrodes was placed on the skin over the adductor pollicis muscle for direct stimulation. A square wave stimulator was used for both direct and indirect stimulation. Either a single stimulus or a train of four stimuli at a rate of 2 Hz for 2 s was delivered for eliciting contractions of adductor pollicis muscle. The impulses were delivered not earlier than once every 10 s. On a few occasions, the stimulation was continued for 6 or 8 s at 2 Hz. Stimulus voltage was kept at 10–15% over that required to produce maximal contraction. The duration of stimulus was 0.2 ms. A resting tension of 200 g was placed on the thumb and contractions were recorded isometrically using a grass polygraph Model P-23 and F.T.-10 transducer. Contractions of opponens pollicis and flexor pollicis were minimized by keeping the thumb in oppoens position and splinting the thumb so as to prevent flexion of the terminal phalanx. Movement of forearm and wrist was prevented by splinting the arm to a wooden board. Blood pressure, heart rate and respiratory rate were recorded.

Smoking, tea and coffee were prohibited 3 h before the experimental procedure.

Administration of drugs

Each volunteer was administered 1–3 mg of tubocurarine to rule out sensitivity to it. A clinical test for detecting atypical pseudocholinesterase was performed as described by Lee-son, Pilon, Nahor & Waud (1975). On subsequent experiments, tubocurarine (0.05 mg/kg) or suxamethonium (0.08 mg/kg) diluted in 10 ml normal saline was injected intravenously. On separate occasions the rate of injection of tubocurarine or suxamethonium was varied.

Results

A variation of 2% was observed in twitch height due to single stimulation of nerve. A variation of 2% occurred in the four twitch heights produced by a train of four impulses when recorded over a period of 10 min without any drug. In any train of four impulses, the ratio of the height of the fourth contraction to the first when expressed as a percentage was always greater than 94%.

Injection of tubocurarine

Injection of tubocurarine (0.05 mg/kg) did not reduce contractions due to single stimuli more than those in control responses. There was no significant difference between the contraction produced by a single stimulus and the first contractions in the train of four stimuli after tubocurarine. There was a stepwise decrease in the second, third and fourth contraction in the train. The mean percentage inhibition of fourth contraction when compared to first was 23 ± 1.8 . The difference in the response before and after tubocurarine is highly significant at 1% level of significance ($n=6$). A maximum depression of fourth contraction occurred between 3 and 5 min after the injection. Complete recovery to control height was noticed 15 min after the injection. There was no significant difference when tubocurarine was injected over a period of 10 or 20 s. If more stimuli were delivered at 2 Hz, no additional differences could be observed. Contractions due to direct stimulation of muscle remained unchanged after tubocurarine. Figure 1 shows a typical effect of injection of tubocurarine intravenously.

Injection of suxamethonium

Injection of suxamethonium reduced the single twitch responses as well as the train of four responses. All the four contractions in the train of stimuli were inhibited equally and there was no significant difference between the height of fourth and first contraction. Whenever suxamethonium produced an inhibition in the train of stimuli delivered indirectly, it also produced an inhibition of single twitch responses. The extent to which suxamethonium produced inhibition, greatly depended on the rate of injection. Slower rate of injection resulted in less inhibition. Suxamethonium injection when given over a period of 10 s was accompanied by an inhibition of about 40% and was preceded by visible fasciculation. Effect of direct stimulation remained unchanged after suxamethonium. The effects of suxamethonium are shown in Figure 2.

Other parameters

Blood pressure, respiratory rate, tidal volume and minute volume remained unchanged after tubocurarine or suxamethonium. A fall in the heart rate by 6 beats/min occurred after injection of suxamethonium. Diplopia, occurred in five subjects after the injection of tubocurarine and remained for 5 min after complete recovery of twitch heights. Three subjects complained of dizziness. Conjunctival hyperemia was noticed in three.

Figure 1 Recording of contractions of the adductor pollicis muscle during the study of tubocurarine. At A indirect stimulation by a train of four, at B indirect stimulation by a single stimulus and at C a direct stimulation by a train four impulses was done. Tubocurarine (0.05 mg/kg) was injected at $\uparrow$. D shows the effect of more than four stimuli at 2 Hz.

Discussion

Ali *et al.* (1970) tested the effect of tubocurarine and suxamethonium on indirectly elicited contractions of adductor pollicis by train of four stimuli. In their study, using a fixed dose of tubocurarine and a stimulus duration of 0.3 m s in conscious volunteers, a highly variable response was obtained. We used tubocurarine on weight basis and a stimulus duration of 0.2 m s since an excessive stimulus duration (Epstein & Epstein, 1973) or inappropriate wave form can cause repetitive nerve firing (Ali & Savarese, 1976). A fairly constant response was obtained in our study although a better method for correlating muscle relaxation should be with dose calculated on basis of body surface area. Tubocurarine (0.05 mg/kg) produced a stepwise decrease in twitch heights of train of four impulses without altering single twitch responses indicating that stimulation at 2 Hz for 2 s is sensitive enough to detect the effects even when single twitch responses remain unaltered. Direct stimulation remained unaltered consistent with the fact that tubocurarine has no direct inhibitory action on muscle itself. Unlike tubocurarine, suxamethonium inhibited

all the four responses. However, the effect of suxamethonium in our study was greatly variable and it was not possible to quantify the data since the degree of inhibition of muscle contraction greatly depended on the rate of injection. From our study it appears that the effect of suxamethonium on train of four impulses in unanaesthetized individuals closely resembles that of large doses in anaesthetized patients (Ali *et al.*, 1970; Lee, 1975); without a Phase II or dual type of block. Like tubocurarine, suxamethonium did not have any direct inhibitory action on muscle. Many methods have been used to assess the degree and type of neuromuscular blockade in anaesthetized as well as unanaesthetized man (Foldes, 1960; Mushin & Mapleson, 1957). Study of evoked responses is by far the best method available. Amongst the evoked responses an inhibition of single twitch responses provides a good method for assessing the degree of neuromuscular blockade but does not indicate the type of neuromuscular blocking agent used. Recording responses due to tetanic stimulation can provide additional information regarding the type of myoneural blockade. Quite frequently a fade in contractions due to tetanic stimulation is considered

Figure 2 Recording of contractions of the adductor pollicis muscle during the study of suxamethonium. At A and B indirect stimulation was done by a single stimulus and a train of four stimuli respectively. At C direct stimulation was done. Suxamethonium (0.08 mg/kg) was injected at $\uparrow$.

characteristic of non-depolarizing block as with tubocurarine. However, Berry (1966), has shown that tetanic fade is not only a function of degree of blockade due to non-depolarizing drugs but also of frequency and duration of tetanus and may even occur in absence of curarization. It has also been shown (Katz, 1965), that fade in tetanic tension may even be absent during 40–50% block after tubocurarine. Thus in order to study the effects of drugs acting at myoneural junction, large amount of drug may be required. Since tetanic stimulation of nerve can be painful it cannot be used in unanaesthetized individuals. The present

method of using a train of four impulses and direct stimulation appears to be the most suitable method for the testing of newer neuromuscular blocking agents in unanaesthetized individuals as effects can be demonstrated in very small doses. The method is also acceptable and there is a minimal discomfort.

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