INTERACTION OF CALCIUM AND POTASSIUM WITH NEUROMUSCULAR BLOCKING AGENTS

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SUMMARY
Dose-response curves for blockade of the indirectly elicited twitch of isolated guineapig nerve-lumbrical muscle preparations were determined for tubocurarine and pancuronium in the presence of potassium 2, 4 and 6 mmol litre\(^{-1}\) and calcium 1, 2 and 3 mmol litre\(^{-1}\). Increases in concentration of either ion decreased the sensitivity of the preparation to both drugs. Over the physiological range of concentrations of potassium and calcium, 36% and 27% variation in dosage can be expected.

Much information is available concerning the influence of the ionic composition of the bathing medium on the electrophysiological behaviour of the neuromuscular junction. For example, calcium has been shown to decrease the degree of depolarization produced by acetylcholine (Ginsborg and Jenkinson, 1976), to accentuate desensitization (Manthey, 1966), and to alter affinity of the receptor for tubocurarine (Jenkinson, 1960)—all postsynaptically. Calcium is known also to have a profound presynaptic effect on the release of transmitter; that is, a nerve impulse will release more acetylcholine if the concentration of calcium is increased (Katz and Miledi, 1965). However, despite this information on the action of calcium on the individual components of the system, we know neither the direction nor the extent of the overall effect. Can the increase in the release of the transmitter produced by the increase in calcium concentration override the concomitant decrease in postsynaptic chemosensitivity? More particularly, will the synapse be more or less sensitive to tubocurarine, and by how much?

A similar problem exists with regard to potassium. Very accurate measurements have been made to demonstrate the dependence of membrane potential and the reversal potential of the end-plate potential on potassium concentration (Katz, 1966). Potassium can be shown to act presynaptically to increase the frequency of miniature end-plate potentials (Ginsborg and Jenkinson, 1976), or to increase the amount of transmitter released. However, as with calcium, the system is too complex to allow deduction about the overall effect of a change in potassium concentration on the dose-response relationship of tubocurarine.

We have attempted direct determination of the dose-response curves for a competitive neuromuscular blocking agent in the presence of varying concentrations of each ion.

METHODS
The experiments were performed using an isolated guineapig nerve-lumbrical muscle preparation. The preparation was suspended in Krebs' solution (composition (mmol litre\(^{-1}\)): sodium 138; potassium 2-6; calcium 1–3, magnesium 1.22; chloride 123; dihydrogen phosphate 1.2; sulphate 1.22; bicarbonate 25; plus glucose, 2.08 g litre\(^{-1}\)) bubbled with oxygen 95%, carbon dioxide 5% and maintained at 37 °C. The nerve was placed in contact with a pair of platinum electrodes and stimulated every 10 s with a shock of 0.3 ms duration and twice maximum intensity. The resulting indirectly elicited twitch response was recorded with an isometric transducer connected to an oscillograph pen recorder.

After isolation, the preparation was equilibrated with a bathing solution of potassium 5.9 mmol litre\(^{-1}\) (the usual value for Krebs' solution) and calcium 1, 2 or 3 mmol litre\(^{-1}\). Alternatively, the concentration of calcium was held at the customary 2.5 mmol litre\(^{-1}\) and the potassium set at 2, 4 or 6 mmol litre\(^{-1}\). Following equilibration, tubocurarine or pancuronium was added in increasing concentrations to give a series of step-wise decreases in twitch height. The results were plotted as twitch height against concentration of antagonist. A sigmoid curve was fitted to the results by an iterative non-linear least squares technique analogous to that used previously in this
laboratory (Waud, 1975), and an estimate of the concentration halving the twitch response—the tubocurarine or pancuronium ED$_{50}$—was obtained. Finally, these ED$_{50}$ values were plotted against the concentration of potassium or calcium in which they were obtained to demonstrate the relationship of the dose of tubocurarine or pancuronium to ionic composition.

RESULTS

Figure 1 shows representative dose–response curves obtained with tubocurarine at three concentrations of potassium. There was a clear shift of the curve to the right with increasing concentrations of potassium; that is potassium increases the dose of tubocurarine required to produce any given depth of block. The results of all such experiments are presented in figure 2, with the corresponding values for pancuronium. Both drugs were affected similarly by changes in concentration of potassium.

Calcium also had a marked effect on the preparation. Figure 3 shows representative dose–response curves obtained with pancuronium at three calcium concentrations. Figure 4 summarizes the results, with the corresponding values obtained with tubocurarine.

Both pancuronium and tubocurarine were affected similarly by changes in concentration of calcium.

The effects of tubocurarine and pancuronium were reversible following washing.
Discussion

Increases in the concentration of either potassium or calcium produced decreases in the sensitivity of the isolated nerve–muscle preparation to both tubocurarine and pancuronium. These results represent the effect of relatively acute changes in concentration of the ions studied.

Each dose–response curve in figures 1 and 3 represents an experiment which took about 6 h to complete. However, it was found that with an acute change of potassium or calcium ion concentration the twitch response shifted rapidly (in a few min) to the new level. In the case of potassium, chronic changes in plasma concentration may produce different effects as the ion redistributes across the cell membrane. Calcium, on the other hand will probably show less difference with chronic changes, since intracellular concentrations appear to be actively maintained at relatively stable (and low) values.

Patients can show considerable variation in sensitivity to competitive neuromuscular blocking agents. For example, Katz (1967) gave tubocurarine 0.1 mg kg\(^{-1}\) to a group of subjects and found that the degree of block ranged from imperceptible to complete. Presumably this variation reflects the interplay of many factors such as end-organ sensitivity, pharmacokinetic processes, and the patient’s physical condition. The first step in sorting out the relative contributions of such a multitude of factors is to examine the effect of each in isolation in a well-controlled system. The present study presents such information for two variables, plasma potassium and calcium ion concentrations. The use of an isolated organ preparation permits a change in the variable of interest without changing others. This may be contrasted with analogous studies in vivo in which, in order to change concentration of potassium, large and repeated doses of diuretics were used (Hill et al., 1978). Such studies are hard to interpret because of the difficulty in determining which of the many effects of the diuretic is responsible for the results observed.

The observations with calcium may be viewed in the framework of the extent of patient-to-patient variation in plasma concentration of this ion. A normal range of 2.1–2.6 mmol litre\(^{-1}\) (Castleman, 1974) for total calcium ion concentration would (since 50% is plasma bound) correspond to 1.06–1.31 mmol litre\(^{-1}\) in our Krebs’ solution which contained no protein. From figure 4 this degree of variation would lead to a change of \(ED_{50}/K_B\) from 2.2 to 2.8, corresponding to about a 27% increase in \(ED_{50}\). The wide range of ion concentration that could accompany pathological states would produce greater alteration in sensitivity to tubocurarine or pancuronium.

In the case of potassium, the normal range is of the order of 3.5–5.0 mmol litre\(^{-1}\) (Castleman, 1974). Figure 2 indicates a corresponding change in dose requirement of tubocurarine or pancuronium from 3.6 to 4.9 units of \(K_B\) or a 36% increase in \(ED_{50}\). Again, the wider range of pathological variations in ion concentration would produce more extensive perturbation of dose requirement.

The present measurements should not be used to determine in advance the dose of a neuromuscular blocking agent, but as background information for titration of the drug against the patient’s response.

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References


**INTERACTION DU CALCIUM ET DU POTASSIUM AVEC LES AGENTS DE BLOCAGE NEUROMUSCULAIRE**

**RESUME**

On a déterminé les courbes dose/réaction pour le blocage de la crispation produite indirectement par des préparations de muscle/nervi lumbriques isolés du coquin d'Inde pour la tubocurarine et le pancuronium en présence de potassium à raison de 2, 4 et 6 mmol litre⁻¹ et de calcium à raison de 1, 2 et 3 mmol litre⁻¹. Les augmentations de concentration de l’un ou l’autre ion ont fait baisser la sensibilité de la préparation à ces deux médicaments. On peut s'attendre à des variations dans le dosage de 36% et de 27% sur la plage physiologique des concentrations de potassium et de calcium.

**WECHSELWIRKUNG VON KALZIUM UND KALIUM MIT NERVENMUSKEL-BLOCKIERUNGSMITTELN**

**ZUSAMMENFASSUNG**

Es wurden Dosis–effektkurven für die Blockade der indirekt ausgelösten Zuckungen bei isolierten nerven–lumbrikalen Meerschweinchen-Muskelpräparaten für Tubocurarin und Pancuronium im Beisein von 2, 4 und 6 mmol Liter⁻¹ Kalium und 1, 2 und 3 mmol Liter⁻¹ Kalzium bestimmt. Erhöhungen der Konzentration des einen oder des anderen Ions haben die Empfindlichkeit des Präparats gegenüber beiden Mitteln vermindert. Über den physiologischen Bereich von Kalium- und Kalziumkonzentrationen kann man mit Dosis-Variationen von 36% und 27% rechnen.

**INTERACCIÓN DEL CALCIO Y DEL POTASIO CON LAS AGENTES DE BLOQUEO NEUROMUSCULAR**

**SUMARIO**

Se determinaron las curvas de respuesta-dosis para el bloqueo de la crispatura indirectamente obtenida de preparaciones musculares del nervio lumbrrical de animales de laboratorio aisladoss, en lo que respecta a la tubocuranina y al pancuronium, en presencia de 2, 4 y 6 mol litro⁻¹ de potasio y de 1, 2, 3 mol litro⁻¹ de calcio. El aumento de la concentración de cualquiera de estos iones disminuyó la sensibilidad de la preparación de ambas drogas. A lo largo de la gama fisiológica de una variación del 36% al 27% en la dosis.