DISOPYRAMIDE AND NEUROMUSCULAR TRANSMISSION

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SUMMARY

The effect of disopyramide on neuromuscular transmission has been studied using the rat isolated phrenic nerve-diaphragm preparation. The response of the muscle to indirect nerve stimulation was decreased in the presence of disopyramide $5.6 \times 10^{-6}$ mol litre$^{-1}$ ($P < 0.05$), total blockade occurring at $5.6 \times 10^{-5}$ mol litre$^{-1}$. Marked augmentation of the response to direct muscle stimulation was recorded in the presence of disopyramide $1.8 \times 10^{-5} - 5.6 \times 10^{-4}$ mol litre$^{-1}$. Disopyramide $5.6 \times 10^{-6}$ mol litre$^{-1}$ caused a leftward shift of the log concentration response for tubocurarine and decreased the antagonist effect of neostigmine.

Although supraventricular and ventricular arrhythmias are often treated with disopyramide, the exact mode of action of the drug has not been characterized fully. An anticholinergic atropine-like action and local anaesthetic effects on nerve conduction have been suggested (Baines et al., 1976). Anticholinergic activity has been demonstrated at nicotinic receptor sites and these include sympathetic ganglion blockade (Mahmoodi et al., 1980). Any interaction between disopyramide and other agents which have an effect at cholinergic (nicotinic) sites may influence the action of neuromuscular blocking drugs used during general anaesthesia. Therefore, it may be informative to examine the effect of disopyramide on neuromuscular transmission.

METHODS

Adult Wistar rats (body weights 240–300 g) were killed by a blow on the head and bled from an incision in the throat. The left phrenic nerve and hemi-diaphragm were dissected (Bulbring, 1946) from a freshly killed animal and suspended in a 50-ml organ bath containing Krebs solution (composition (mmol litre$^{-1}$): NaCl 118, KCl 4.7, CaCl$_2$ 2.5, MgSO$_4$ 1.2, NaHCO$_3$ 1, Na$_2$PO$_4$ 1 and glucose 11.1) maintained at 37 °C. Oxygen 95% and carbon dioxide 5% were bubbled through the Krebs solution.

The nerve or muscle was stimulated for a 30-s period using a supramaximal rectangular wave stimulus, 12 times per min. A 0.2-ms pulse width was used for indirect stimulation through the nerve and a 2-ms pulse width for direct muscle stimulation. The contraction responses of the muscle were detected with a force displacement transducer and recorded using an ultraviolet light recorder (S. E. Labs).

The responses of the preparation were allowed to stabilise for 45 min before control recordings were obtained. During this period of stabilization the Krebs solution was changed every 15 min. Log concentration–response curves for disopyramide $1 \times 10^{-7} - 1.8 \times 10^{-3}$ mol litre$^{-1}$ using indirect nerve stimulation were obtained by adding increments of disopyramide to the bath at 12-min intervals. The experiment was repeated using direct muscle stimulation and fresh preparations. The same concentrations of disopyramide were used but, in order to eliminate the effect of stimulation of motor nerve endings in the muscle, tubocurarine was added to the bath to give a concentration of $4 \times 10^{-5}$ mol litre$^{-1}$. This concentration of tubocurarine had previously been shown to abolish neuromuscular transmission.

In a second series of four experiments, log dose–response curves for tubocurarine were obtained by adding increments of tubocurarine at 15-min intervals for a 3-min contact time which was ended by washing four times with Krebs solution over a period of 12 min. Tubocurarine was added to the preparations to give concentrations within the range $1.6 \times 10^{-7} - 2.6 \times 10^{-6}$ mol litre$^{-1}$. The following combinations and concentrations of drugs were...
used. Five fresh preparations were used for each investigation.

(1) Tubocurarine $1.6 \times 10^{-7} - 2.6 \times 10^{-6}$ mol litre$^{-1}$.

(2) Tubocurarine $1.6 \times 10^{-7} - 2.6 \times 10^{-6}$ mol litre$^{-1}$ plus disopyramide $5.6 \times 10^{-6}$ mol litre$^{-1}$.

(3) Tubocurarine $1.6 \times 10^{-7} - 2.6 \times 10^{-6}$ mol litre$^{-1}$ plus neostigmine $5.6 \times 10^{-8}$ mol litre$^{-1}$.

(4) Tubocurarine $1.6 \times 10^{-7} - 2.6 \times 10^{-6}$ mol litre$^{-1}$ plus neostigmine $5.6 \times 10^{-8}$ mol litre$^{-1}$ plus disopyramide $5.6 \times 10^{-8}$ mol litre$^{-1}$.

Disopyramide (experiments 2 and 4) was allowed a contact time of 45 min before either neostigmine or tubocurarine was added to the bath. The concentration of neostigmine used ($5.6 \times 10^{-8}$ mol litre$^{-1}$) was the concentration which, when used alone, produced a maximum response to phrenic nerve stimulation; at greater concentrations of neostigmine the response to phrenic nerve stimulation was decreased.

RESULTS

The effects of different concentrations of disopyramide are shown in figure 1. In the presence of $5.6 \times 10^{-8}$ mol litre$^{-1}$ the muscle response to phrenic nerve stimulation decreased to 70% (SEM 13.8) of the control response ($P<0.05$), but the developed tension returned to baseline at concentrations between $5.6 \times 10^{-6}$ and $1.8 \times 10^{-4}$ mol litre$^{-1}$. At greater concentrations of disopyramide the response to indirect stimulation was again evident and total blockade occurred in the presence of disopyramide $5.6 \times 10^{-4}$ mol litre$^{-1}$. Disopyramide $5.6 \times 10^{-6}$ mol litre$^{-1}$ produced no significant depression of the response to direct muscle stimulation, but at concentrations between $1.8 \times 10^{-4}$ and $5.6 \times 10^{-4}$ mol litre$^{-1}$ there was marked augmentation of the response. The response of the muscle to indirect nerve stimulation was fully blocked in the presence of tubocurarine $5.6 \times 10^{-4}$ mol litre$^{-1}$.

The concentration–response curves for tubocurarine alone and in the presence of neostigmine, disopyramide and disopyramide with neostigmine are shown in figure 2. Disopyramide $5.6 \times 10^{-6}$ mol litre$^{-1}$ caused a leftward shift of the log dose–response curve for tubocurarine. The response curve for tubocurarine and disopyramide combined with neostigmine was to the left of the curve for tubocurarine and neostigmine alone. Neostigmine did not alter the reduced response
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 associated with disopyramide \(5.6 \times 10^{-6}\) mol litre\(^{-1}\) in the presence of tubocurarine \(1.6 \times 10^{-7}\) mol litre\(^{-1}\). There was no detectable decrease in the response in the presence of tubocurarine \(1.6 \times 10^{-7}\) mol litre\(^{-1}\) alone.

Disopyramide \(1.0 \times 10^{-7} - 5.6 \times 10^{-4}\) mol litre\(^{-1}\) did not alter the pH of the gassed Krebs' solution.

**DISCUSSION**

Disopyramide has been shown to be effective in the management of atrial and ventricular arrhythmias (Mokler and Van Arman, 1962; Sekiya and Vaughan Williams, 1963; Dean, 1975) and may be considered for use in the management of cardiac arrhythmia occurring during general anaesthesia. Furthermore, patients who are being treated with disopyramide may present for general anaesthesia.

Disopyramide has been shown to possess anticholinergic atropine-like properties (Baines et al., 1976), but an action at nicotinic receptor sites was not demonstrated in *in vivo* studies (Baines et al., 1976). Byrne and colleagues (1981) identified blockade of transmission in sympathetic ganglia and, in the present study using the rat isolated phrenic nerve–diaphragm preparation, disopyramide has been shown to decrease neuromuscular transmission. The decrease in neuromuscular transmission may result from more than one mechanism, but the involvement of a post-junctional anticholinergic (anti-nicotinic) action is likely (Byrne et al., 1981). In addition to an anticholinergic mechanism, other effects of disopyramide which have been reported may be involved at high concentrations; these include a local anaesthetic action (Baines et al., 1976) or an alteration in the control of calcium ion movement (Nayler, 1976). Disopyramide decreases the capacity of superficially located binding sites to accumulate calcium ions, but the influence of this change on the inward carrying calcium current has not been explored.

The depression in response to nerve stimulation in the presence of disopyramide \(5.6 \times 10^{-4}\) mol litre\(^{-1}\) cannot be a result of muscle depression because it is associated with marked augmentation of the response to direct muscle stimulation.

A mean peak serum concentration of \(5.6 \mu g ml^{-1} (1.3 \times 10^{-5}\) mol litre\(^{-1}\)) was recorded after disopyramide 100 mg was given i.v. over 5 min (Hillis et al., 1976). However, the serum concentration following i.v. injection decreases rapidly initially (half-life 3 min), although the subsequent decrease is much slower (half-life
The use of disopyramide alone is unlikely to lead to overt neuromuscular blockade, assuming a similar concentration–effect ratio for disopyramide in man and rat; nonetheless the concentration of tubocurarine which was required to decrease the response of the diaphragm approximately 50% was halved by the addition of disopyramide 5.6 x 10^{-6} \text{mol litre}^{-1}. Therefore, the possibility that the simultaneous use of disopyramide and other drugs which possess anticholinergic (antinicotinic) properties may decrease neuromuscular transmission must be considered. Furthermore, the effect of disopyramide on neuromuscular transmission, in the concentrations tested here, is most marked in the presence of low concentrations of tubocurarine. Therefore, disopyramide may increase the residual impairment in neuromuscular transmission at the termination of anaesthesia.

**REFERENCES**


