THE INFLUENCE OF SOME ANTIFUNGAL ANTIBIOTICS ON NEUROMUSCULAR TRANSMISSION

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The influence of the polyene antifungal antibiotics pimaricin, amphotericin A and B and nystatin, on neuromuscular transmission has been studied.

In presence of these antibiotics both direct and indirect electrical stimulation is found to cause varying degrees of contracture and diminished excitability of the musculature. This is in contrast to the effect of Hamycin, another polyene antibiotic which produces loss of excitability without any initial contracture of the diaphragm.

Certain antibiotics have been shown to produce neuromuscular block, both in experimental animals and in humans. Intraperitoneal administration of neomycin has been followed by respiratory insufficiency or apnoea ; streptomycin has caused neuromuscular block in experimental animals and in intercostal nerve preparations of human and is strongly incriminated in causing the muscular weakness and visual difficulty as also post-operative paralysis by neuromuscular blockage (Fisk, 1961, Bush, 1961). Polymyxin B is also reported to exhibit blocking action on the muscle end plate (Sabawala and Dillon, 1959). The following communication deals with the effect of certain antifungal antibiotics on the neuromuscular junction as studied by the rat phrenic nerve diaphragm preparations.

METHODS

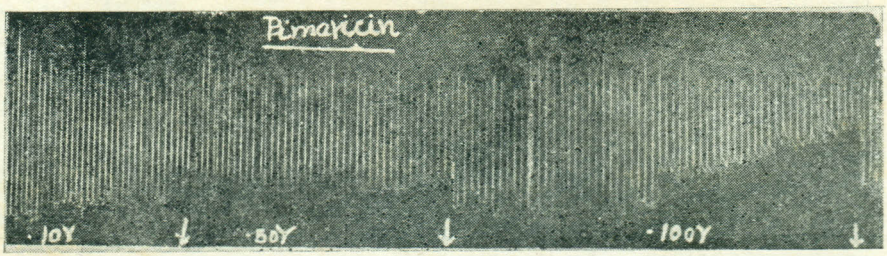
The antibiotics studied were, pimaricin, amphotericin A and B, and nystatin. Their effects have been compared with those of hamycin reported earlier (Sirsi, 1963).

The required concentrations of the antibiotics were prepared in propylene glycol and further dilutions in water.

Phrenic nerve diaphragm preparations were made as described by Bulbring (1946) and were suspended in a bath of 75 ml of aerated Tyrode's solution which contained twice the amount of glucose as stated in original

formula. Contractions of the diaphragm were induced by supramaximal stimulations of the phrenic nerve or the diaphragm, as required, at the rate of 8/min. Muscle contractions were recorded by a frontal writing lever. When the muscle contractions gave constant height, the drugs were added to the bath. The effect of the solvent, propylene glycol by itself, in the volumes used with drug, was similarly noted.

Pimaricin.—Contracture of the musculature, though to varying extent is observed on both direct and indirect stimulation in presence of the antibiotic, the nerve stimulation showing the greater effect. The recovery after wash was fairly quick in both (Fig. 1, a, b). Besides contracture, a depression of the response to direct electrical stimulation was also observed at 100 ug/ml concentration (Fig. 1. b).



a.

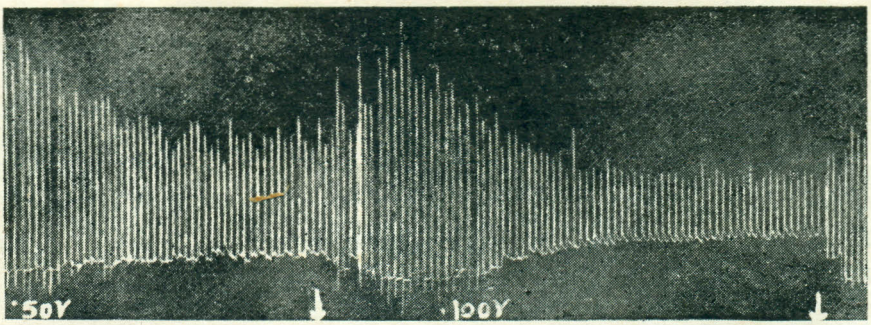


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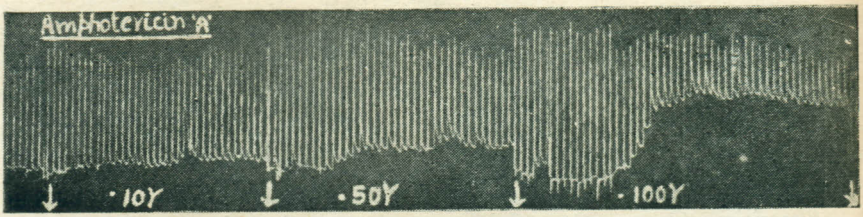
Fig. 1. Effect of pimaricin on; (a) rat phrenic nerve diaphragm preparation. Stimulation through nerve 8/min. at arrow specimen washed, (b) direct stimulation of diaphragm.

Amphotericin A and B.—The general trend of reaction was similar to those of pimaricin, excepting that the contracture appeared to be more prominent on direct stimulation (Fig. 2 b).



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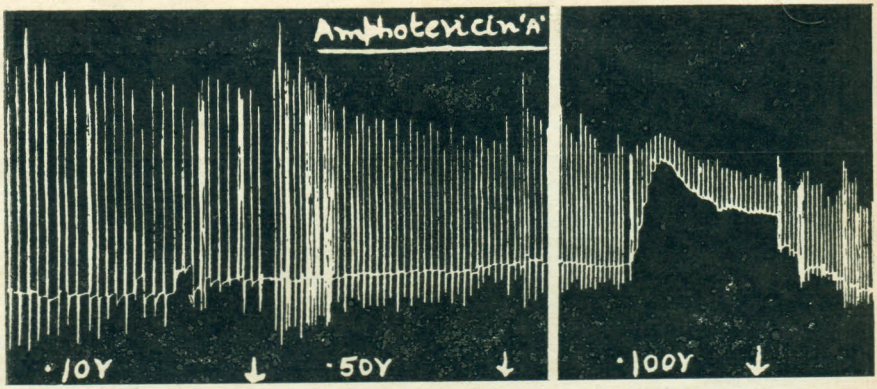

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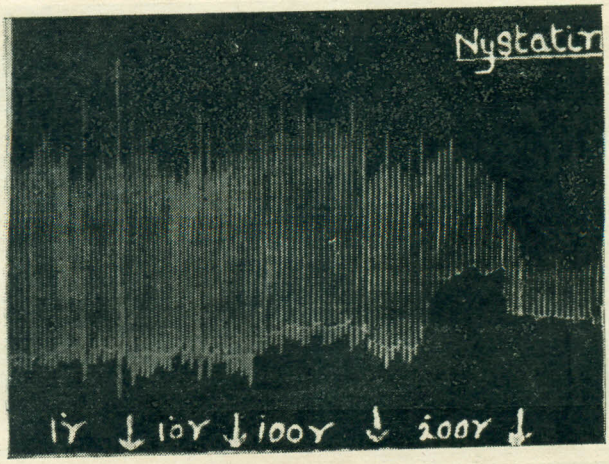
Fig. 2. Amphotericin A and the rat diaphragm on, (a) indirect stimulation (b) direct stimulation.

Nystatin.—The effect closely resembled those of amphotericin, the direct stimulation causing the greater contracture (Fig. 3. b).

Propylene glycol.—The maximum amount of the solvent used at a time with the drugs was 0.75 ml. The solvent even at 1 ml, in the bath, exhibited no contracture of the diaphragm on electrical stimulations. The slight effect observed was more in the direction of diminished excitability with no contracture (Fig. 4, a.b).

The addition of the drug solutions to the perfusion bath did not alter the pH. of the Tyrode solution, which remained constant at 7.6.

Hamycin.—The influence of this polyene antifungal antibiotic is described in an earlier paper (Sirsi, 1963). Reduction of excitability to almost complete loss of contractility on prolonged contact and absence of contracture on both direct and indirect stimulations were the results observed.



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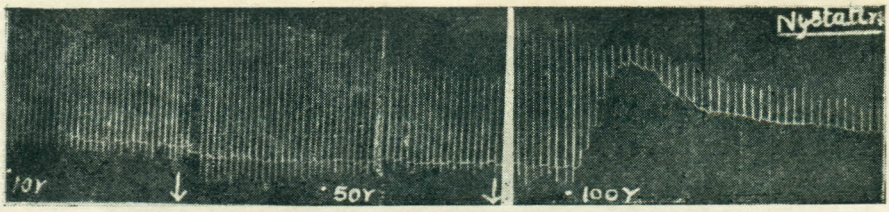

b.

Fig. 3. Nystatin and diaphragm on, (a) indirect stimulation, (b) direct stimulation.

Amongst these antifungal antibiotics, the chemical structure indicates pimaricin and amphotericin A to be tetraenes ; nystatin, a dienetetraene; amphotericin B and hamycin as heptaenes.

The results show that none of the compounds exhibit curariform activity but manifest varying reactions on the musculature. Hamycin is a potent inhibitor of excitability and causes no contracture of the diaphragm. All the other compounds induce contracture on stimulation, the difference from each other being only of a quantitative nature. Chemical structure and biological activity do not seem to be closely related in these group of compounds, since hamycin, a heptaene causes loss of excitability while amphotericin B, another heptaene induces contracture.

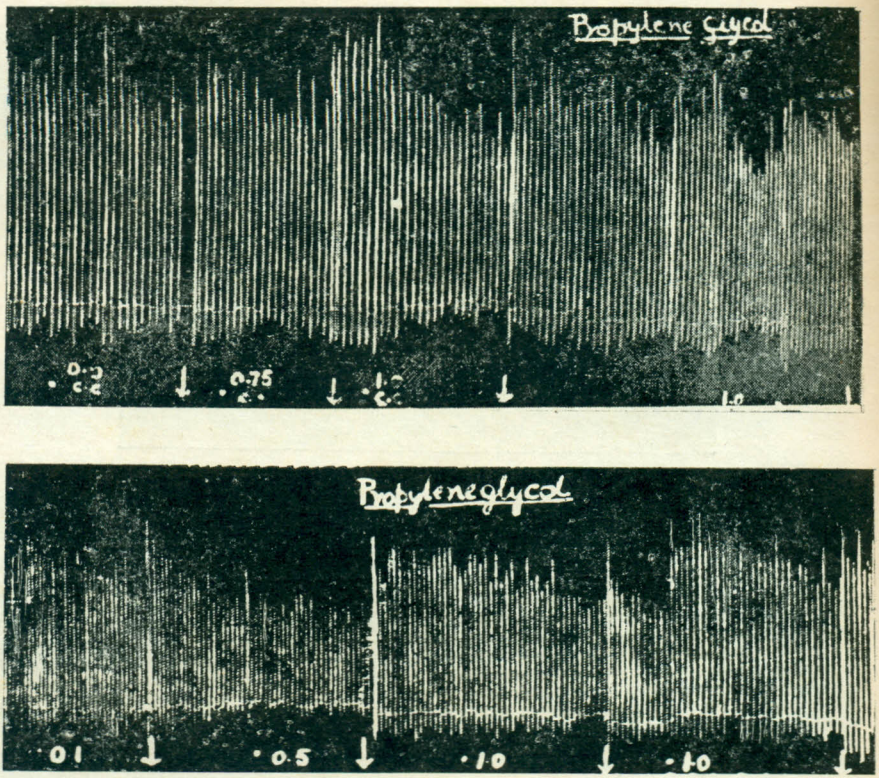

Fig. 4. Propylene glycol and rat diaphragm on; (a) indirect stimulation. The second 1·0 ml. was left in contact with the muscle for 12 min. after 3 min. initial stimulation. Prolonged contact had no effect, (b) direct stimulation.

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REFERENCES

Bulbring, E., (1946). *Brit. J. Pharmacol.*, **1**, 38.

Bush, G.H. (1961). *Brit. Med. J.*, **1**, 557.

Fisk, G.C. (1961). *Brit. Med. J.*, **1**, 556.

Sabawala, P.B., and Dillon, J.B. (1959). *Anaesthisiology*, **20**, 659.

Sirvi, M. (1963). *Ind. Jour. Pharmacy*, **25**, 53.