NEUROMUSCULAR ACTIONS OF SOME NEWLY SYNTHESIZED LIGNOCAINE ANALOGUES*

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In the present study neuromuscular effects of lignocaine and of 6 newly synthesized analogues of lignocaine have been studied on different skeletal muscle—nerve preparations. The neuromuscular block produced by lignocaine and compounds D and F appears to be similar as reported for curare but the same does not appear to be true for compounds A, B, C, and E which seem to act by persistant depolarisation. An attempt has also been made to corelate these actions with the chemical structure and the local anaesthetic activity.

Neuromuscular blocking action of procaine was demonstrated by Harvey (3), Jaco and Wood (4) and Straugham (6). Lignocaine is comparatively a new local anaesthetic which is different in chemical structure to the conventional local anaesthetics of procaine series. Recently Trivedi and Dalal (7) synthesized a series of new local anaesthetics as analogues of lignocaine, 17 of them were screened in our laboratory for their local anaesthetic activity (5). Of these 6 were selected for detailed pharmacological study. Lignocaine has been acclaimed as an all round potent local anaesthetics agent, but there is scanty literature regarding its general pharmacological actions and much less its neuromuscular activity. It was therefore thought proper to investigate the neuromuscular actions of lignocaine and compare it with some of the newly synthesized analogues of lignocaine, with a view to elucidate the mechanism of action.

The chemical structure of different compounds and their code name have been supplied in Table 1.

All the compounds used were soluble in water.

MATERIAL AND METHODS

The skeletal muscle-nerve preparations employed in these experiments were as follows.

Rectus Abdominis of Frog :—The method was essentially the same as described by Burn (2). Contractions of uniform height were induced with acetylcholine—(1 μg./ml.), left in contact for a period of 90 second. The drugs were allowed to remain in contact with the muscle for 60 second, before eleciting contraction with acetylcholine.

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*1. This formed part of the thesis of M. A. Patel for Ph. D. (Pharmacology) of Gujarat University.

2. Paper read at the IX annual conference (1963), of the Association of Physiologist and Pharmacologist of India.

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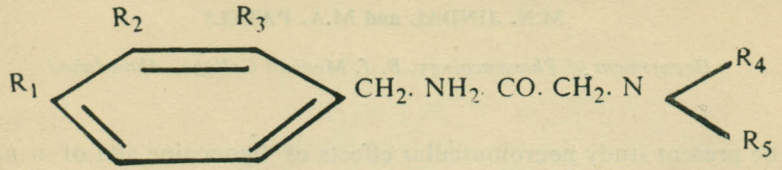
TABLE 1

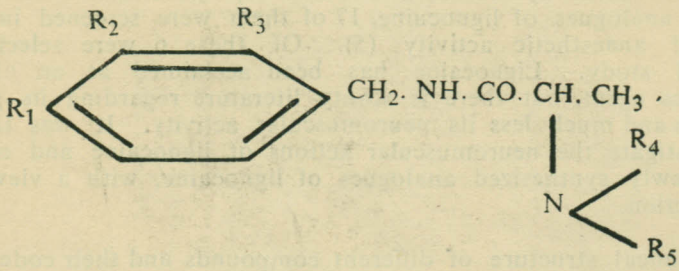
Chemical structure of local anaesthetics

Acetamide compounds



Code No.	R_1	R_2	R_3	R_4 and R_5
A	—	—	Cl	Diethyl
B	—	—	CH_3	Morpholinyl
C	Cl	Cl	—	Piperidinyl

(2) *Propionamide compounds*



Code No.	R_1	R_2	R_3	R_4 and R_5
D	CH_3	—	CH_3	Diethyl
E	Cl	—	—	Morpholinyl
F	CH_3	—	CH_2	Piperidinyl

Having seen the effect of the drug, the bath was washed out several times till the normal contractions were restored.

Phrenic nerve diaphram of rat :—Hemi diaphragm of rat with the phrenic nerve attached was dissected out and suspended in a bath of 50 ml capacity containing Oxygenated Tyrode solution with double the amount of dextrose as suggested by Burn (1). Contractions were induced by stimulating the phrenic nerve and also directly by means of impulses from a square wave stimulator at 0.2 to 2 *m.a.* current of 0.2 *m.s.* duration not more than 6 times per minute.

Dog Gastrocnemius sciatic nerve :—The method was essentially the same as described by Burn (1) except that dog has been used in place of cat. Contractions were induced by stimulating the nerve and also directly by means of impulses from a square wave stimulator as in the case of phrenic nerve diaphragm of rat. Retrograde injections of drug solutions were made through the cannulated right iliac artery and the effects recorded on a moving drum.

RESULTS

Rectus Abdominis of frog :—Graded doses of the solutions were added to the bath ranging from 1 μg. to 1 mg./ml. The results elicited with different compounds may be grouped into two classes.

(*i*) those which potentiated the acetylcholine induced contractions with all the doses *i.e.*, compounds A, C and E.

(*ii*) Those which inhibited in all the doses *i.e.*, compounds B, D, F and L.

Typical results with compound A are shown in Figure 1.

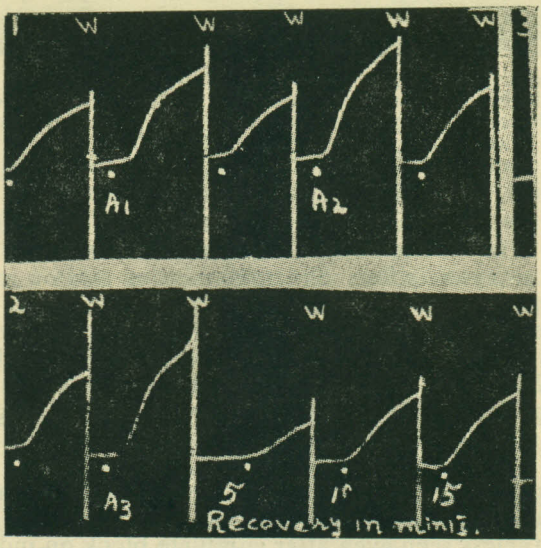


Fig. 1. Frog rectus abdominis suspended in a 10 ml. bath contaning oxygenated frog Ringer solution at room temperature. Contractions to acetylcholine (1.0 μg/ml). Numbers indicate time interval in minutes. Acetylcholine was left in the bath and then washed out. At A, 10; $A_2$50; and $A_3$200 μ/ml of compound A.

Phrenic nerve diaphragn of rat :—Graded doses of the drugs were administered ranging from 0.1 μg. to 100 μg./ml. The results may be classified in two groups.

1) Those which potentiated the contractions in small doses and inhibited in larger doses *i e.*, compounds A, B, C, and E.

2) Those which inhibited the contractions in all the doses *i.e.*, compound D, F and L.

Typical results with compound C have been illustrated in Figure 2. The equipotent doses of these compounds namely A, B, C, D, E, F and L, causing hundred percent inhibition of contraction were 10, 100,25,100,50,5 and 50 μg./ml respectively.

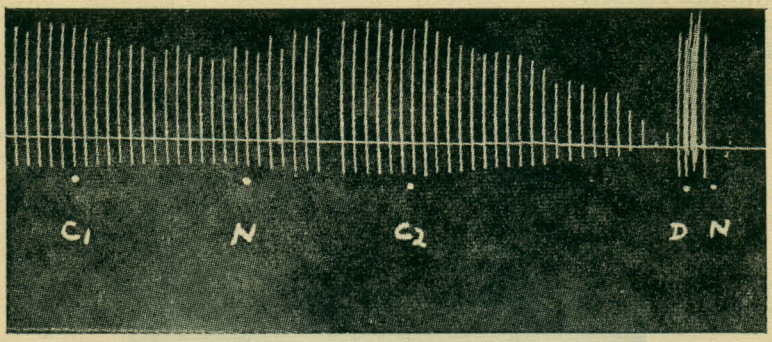


Fig. 2. Rat diaphragm-phrenic preparation. Contraction induced by indirect stimulation of the phrenic nerve or by direct stimulation of the muscle At C_1 10 and $C_2$25μ./ml. of compound C. At N 10μ./ml. neostigmine. At D. Direct stimulation.

Neostigmine 10 μg./ml was wholly ineffective in counteracting the block produced by these compounds The muscle however, responded maximally to direct stimulation. The muscle recovered completely for indirect stimulation also on repeated washing though the time of recovery varied with the compound and the dose.

Gastrocnemius sciatic nerve of dog :—Graded doses of the drugs were given ranging from 1 mg to 20 mg./kg body weight. With smaller doses either there was slight stimulation (Compound B and E) or no effect (A and C). With higher doses most of the drugs produced inhibition of muscular contraction.

Partial block produced by these compounds (except compound F) was antagonised with neostigmine but complete block remained uneffected. The response to direct stimulation was nevertheless seen even after complete block on indirect stimulation. The results with compound D have been illustrated in Figure 3.

DISCUSSION

The present experiments with lignocaine and six of its analogues on different types of skeletal muscle preparations show that the character and mechanism of action of all these local anaesthetics is not the same. Lignocaine and its 6 analogues may be conveniently divided into two groups. Group I comprises of lignocaine and compounds D & F.

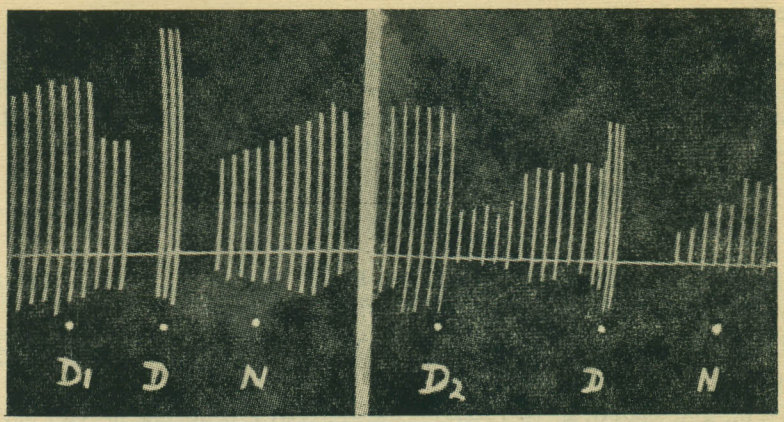


Fig. 3. Dog gastrocnemius Sciatic preparation. Contractions induced by indirect stimulation of the sciatic nerve or by direct stimulation of the muscle. At D_1 5 mg. and D_2 10 mg./kg of compound D. At N, 0.1 mg./kg of neostigmine. At D, direct stimulation.

These are the compounds which have shown inhibition of muscular contractions in all types of preparations and with all the doses administered. Group II comprises of compounds A, B, C and E which have shown potentiation with smaller doses in a majority of experiments. Higher doses of these compounds have shown inhibition in majority of experiments.

In all the experiments with all the compounds the muscle continued to respond on direct stimulation at a time when it was found to be nonresponsive to indirect stimulation.

Neostigmine was able to counteract the partial block produced by some of the compounds of the first series in dog's gastrocnemius sciatic nerve prepration but it was wholly ineffective in counteracting complete block produced by these compounds including lignocaine.

From these observations it therefore seems likely that the mechanism of neuromuscular block produced by compounds in Group I *i.e.*, lignocaine and compounds D and F is curare like in nature *i.e.* through receptor blockade. The neuromuscular blockade by compounds in Group II *i.e.*, A, B, C and E however, appears to be through persistant depolarisation, which is indicated by initial stimulation of muscular contractions with smaller doses and paralysis with higher doses.

It is difficult to corelate the neuromuscular actions with the chemical structure of these compounds mainly because the series is small. It may however, be observed that compounds A, B and C which stimulate muscular contractions are all acetamide derivatives, while compounds D and F which depress muscular contractions with all the doses and in all types of preparations are propionamide compounds. The only exception is compound E, which though a propionamide derivative stimulates muscular contractions

of rectus abdominis in all the doses and diaphragm of rat and gastrocnemius of dog in—smaller doses.

As regards relationship between local anaesthetic potency and neuromuscular blocking activity, we have observed that the compounds namely F and A which showed the most potent surface and intradermal anaesthetic activity (5) have also shown potent neuromuscular blocking actions, though the same cannot be said with other compounds of this series.

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