NEUROMUSCULAR BLOCK WITH LIGNOCAINE *

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That procaine may block neuromuscular transmission, is an old observation of the years following its introduction in 1904.[9,13] This observation was later reinvestigated by Harvey,[6] who showed that procaine possessed properties resembling the antidepolarizing relaxants—that it resembled d-tubocurarine (dTC) in its action on the muscle end plate. Confirmation of this may be found in the work of Jaco and Wood[7] and Petersen,[12] and of Gjone,[4] who also reviewed the subject.

In this preliminary report it is intended to communicate some findings of a similar investigation on the newer local analgesic agent lignocaine (Xylocaine). Special attention was devoted to discovering whether the antidotes to dTC (such anticholinesterases as neostigmine and physostigmine) were as ineffective in relieving lignocaine block as they are in opposing procaine block.

Method

All previous investigations on this subject appear to have been made with nerve-muscle preparations. Since procaine may be shown to interfere with the production and release of acetylcholine in addition to blocking the response of the postsynaptic region to acetylcholine,[6,11] a nerve-muscle preparation will indicate only the combined effect of these two actions without indicating the relative importance of either. This apparent disadvantage may be overcome by using a preparation of the frog's rectus abdominis in which the addition of a constant dose of acetylcholine to a muscle bath replaces nerve stimulation. Thus the effect of the drug under test may be studied on the post-synaptic site only.

Such a preparation was therefore employed, using the upper portion of half the rectus abdominis taken from the South African clawed toad, *Xenopus laevis*. This was placed in a bath of 4-5 ml. capacity containing aerated Ringer's solution. Acetylcholine, in suitable dilution, was freshly prepared from a refrigerated acetate-buffered stock solution. This was added to the bath in submaximal dose to stimulate the muscle, and was allowed to act for 1 minute. Following this the muscle was washed with 3 changes of bath contents at half-minute intervals, and allowed to rest for 3 minutes, the whole cycle taking 5 minutes. Test drugs were allowed to act for $2\frac{1}{2}$ minutes before acetylcholine stimulation. All additions to the bath were made in volumes of 0·1 or 0·2 ml. from micropipettes.

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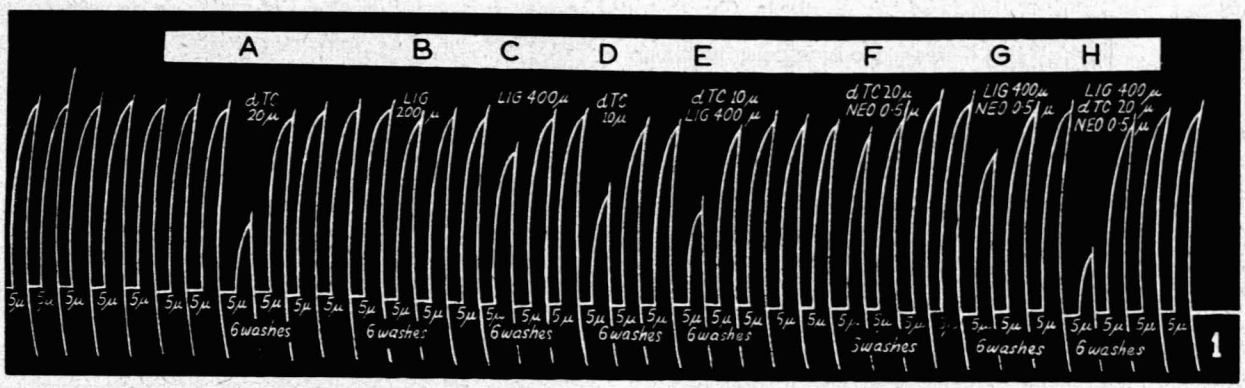

Fig. 1. Kymograph recording of frog rectus abdominis preparation. Contractions of muscle upwards from base line. Figures below base line indicate (constant) dose of acetylcholine added to bath. For further explanation see text.

The results were recorded on a smoked drum with a direct writing lever using a magnification of 4.

Results

To summarize the findings, a special record from a single muscle was made (Fig. 1) illustrating most of the salient features of the action of lignocaine, including its interaction with dTC and neostigmine, as follows:

(*a*) Lignocaine has a weak neuromuscular blocking action when compared with dTC. Here comparison is made between dTC, 20 μg and 10 μg, (A and D) with lignocaine, 200 μg and 400 μg, (B and C). It is found that these muscles show a fairly wide variation in sensitivity to the local analgesic; in the present case the blocking effect of lignocaine on the end plate might be about 1/60 that of dTC. In other muscles examined, a slight block (as in B) might be produced by 75 μg of lignocaine, with a lignocaine/dTC sensitivity ratio of 1/15.

(*b*) Lignocaine potentiates the blocking effect of dTC, shown by comparing contractions D and E. This is probably the natural consequence of the ability of both dTC and local analgesics to prevent depolarization of the plasma membrane.[5,14]

(*c*) Neostigmine readily antagonizes the blocking action of dTC: there is a most marked difference between contractions A and F: in both, 20 μg of dTC had been added to the bath, but with the addition of 0·5 μg of neostigmine in F.

(*d*) Neostigmine does not antagonize the blocking action of lignocaine. This is shown in contraction G, which is about 4% greater than contraction C (a difference of little significance). However, the depression relative to the preceding normal contraction is about 8·3% in C, and nearly 24% in G. Other preparations have been found to show a more marked increase in lignocaine block of the neostigmine-potentiated contraction. In all, the effect resembles that described with procaine and neostigmine in mammalian muscle by Jaco and Wood.[7]

(*e*) That the powerful antidote action of neostigmine for dTC is abolished after addition of lignocaine is shown in contraction H. In fact, the height of H is almost 17% less than that of A, whilst the depression relative to the preceding contraction is even greater.

DISCUSSION

It is not proposed here to discuss the nature of this paradoxical action of neostigmine on two drugs that appear to have a similar antidepolarizing myoneural blocking effect. The fact has been clearly established for procaine with physostigmine,[6] and procaine and neostigmine.[7,4] The present investigation indicates a similar behaviour with lignocaine and neostigmine. Further, it now appears possible that this potentiation of local analgesic neuromuscular block by neostigmine is largely a postsynaptic effect, without dependence on any interference with acetylcholine release at presynaptic terminals.

Although the nature of this interaction does not seem to be widely appreciated, it is nevertheless not without clinical significance. (A recent text-book[10] devoted to the complications of local anaesthesia makes no mention of it.)

It is known that patients with myasthenia gravis tolerate local anaesthesia badly.[6] Although this may be due to the extreme sensitivity of these patients to antidepolarizing muscle relaxants, Harvey[6] suggested that a probable explanation might also be that these patients are pre-treated with relatively large doses of neostigmine-like drugs. Certainly it would seem unwise to treat muscular weakness in a myasthenic immediately after the use of local analgesics by further injections of anticholinergic drugs.

During general anaesthesia, intravenous procaine or lignocaine may be given together with muscle relaxants in various circumstances. Under these conditions, reversal of residual curarization at the end of operation may be hazardous, and indeed a case was recently seen here in which prolonged profound paralysis followed the use of neostigmine in a patient who had received dTC and lignocaine.

It is not only with dTC or gallamine that this hazard may exist, since the serum esterase responsible for splitting suxamethonium is also inhibited by most local analgesics,[8] including lignocaine.[1] Through this action paralysis may be prolonged, especially in man.[2]

Finally, this same esterase rapidly destroys procaine[8] and probably also lignocaine, although appreciably more slowly.[15] Since neostigmine inhibits this enzyme, procaine hydrolysis is retarded by neostigmine.[3] Generally speaking, therefore, the use of a 'cocktail' of relaxant, local analgesic and neostigmine may lead the compounder into a tight corner; not only may an intense paralysis result, for which there appears to be no antidote, but the hydrolysis of the drugs producing this paralysis is greatly retarded, thus prolonging relaxation. This is a situation to be avoided!

SUMMARY

Lignocaine is found to be a weak neuromuscular blocking compound, apparently resembling curare in its action. Lignocaine will potentiate curare paralysis, but curare antagonists tend to intensify its paralyzing power. Curare antagonists also seem to be unable to reverse curare paralysis in the presence of lignocaine.

Some clinical implications of these observations are discussed.

SAMEVATTING

Deur gebruik te maak van 'n padda rectus abdominis preparaat, is die neuromuskulêre blokkende werking van lignocaine ondersoek. Dit kom voor of lignocaine die werking van procaine op dié gebied naboots daar dit 'n swak neuromuskulêre blokkende middel is, en dat dit 'n curare verlamming potensieer. Maar dit blyk dat middels wat die curare verlamming inhibeer, geneig is om die lignocaine-verlamming te vererger.

Curare word nie geredelik deur die anti-curare-middels geïnhibeer in die teenwoordigheid van lignocaine nie.

Die kliniese toepassing van hierdie feite sluit in die toediening van plaaslike verdowingsmiddels aan pasiënte met ‚Myasthenia Gravis' en die versigtige gebruik van plaaslike verdowings tesame met verslappers.

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