OXYTOCIC EFFECT OF LIGNOCAINE AND ITS RECENTLY SYNTHESIZED ANALOGUES

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Local anaesthetics as a group possess spasmolytic effect on the smooth muscles (2). Uterine muscle though basically a smooth muscle organ, differs from other smooth muscle organs in many respects. Physiologically it is more under the control of sex hormones than the autonomic nervous system. There exists wide species variation in the responses to autonomic nervous stimulation. Pharmacologically the response of uterine muscle to drugs is independent of its innervation and varies markedly according to the menstrual or oestrous cycle, stage of gestation or pregnancy and the species of animals.

Many times the responses of drugs on the uterus are independent and different than those on other smooth muscle tissues elsewhere. The same is true with local anaesthetics. Procaine has been shown to stimulate the smooth muscle of rabbit ileum in small doses and depress it in larger doses (1). Uterus however, remains uneffected with procaine but is sensitised to pituitrin (4). The older local anaesthetic, cocaine has a similar effect on the intestinal musculature but the reactions of the uterus to cocaine appear confusing (7). Miller (5) observed that in a dilution of 1 in 10,000 it acts like epinephrine i.e. augmenter and depressor depending on the animal and the state of pregnancy but according to Thiens (8) 50% of the uterii responded inversely to the two agents. It is thus clear that there is no definite agreement regarding the action of local anaesthetics on the smooth muscles in general and uterus in particular.

The present study was undertaken to investigate the effect of Lignocaine and its 6 newly synthesized analogues (9) on the isolated uterine strips of guineapig and rat.

MATERIALS AND METHODS

Fully grown virgin guineapigs and albino rats were used. Animals were procured originally from Haffkin's Institute and then reared in our own laboratory.

Animals were sacrificed by a blow on head and then bled by cutting one of the carotid arteries. The abdomen was opened and one of the uterine horns was dissected free from the fat and connective tissue. The uterus was then suspended in a 50 ml. bath containing oxygenated tyrode solution at 32°C. The normal rhythmic movements were recorded on a slowly moving drum. The effect of a single dose was recorded for 3 minutes and an interval of 5 minutes was allowed between the successive

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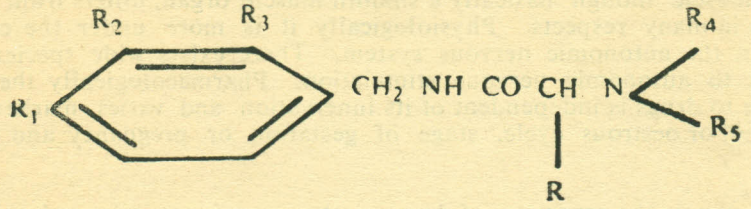
doses. Minimum of 5 experiments were peformed at each dose level and with different compounds.

The chemical structure and the code number of local anaesthetic compounds is given in Table 1. All the compounds were made into solution with distilled water.

TABLE 1

Chemical structure of local anaesthetics



Code No.	R	R_1	R_2	R_3	R_4 & R_5
A	H	—	—	Cl	Diethyl
B	H	CH_3	—	CH_3	Morpholinyl
C	H	—	Cl	—	Piperidinyl
D	CH_3	CH_3	—	CH_3	Diethyl
E	CH_3	Cl	—	—	Morpholinyl
F	CH_3	CH_3	—	CH_3	Piperidinyl

RESULTS

Graded doses of local anaesthetic compounds were administered ranging from 0.2 to 200 μg./ml. On the guineapig uterus stimulant effect was seen with all the compounds including Lignocaine. Quantitatively the effect varied with the compound. The maximum effect was seen with Compound B and Lignocaine. Most of the compounds showed a stimulant effect on the uterine tone and motility with all the doses used except Compounds A and F which showed stimulant effect with smaller doses and depressant effect on the tone and motility of the uterine muscle with larger doses. The stimulant effect was generally related to the dose. With higher doses such as 100 μg./ml. of Compound B and Lignocaine, the uterine-muscle was rendered spastic. Typical reasponses are shown in Figures 1 & 2.

The effect of these compounds on the rat uterus was different than that observed on the guineapig uterus. Compounds A, B, C and D produced depression in the height

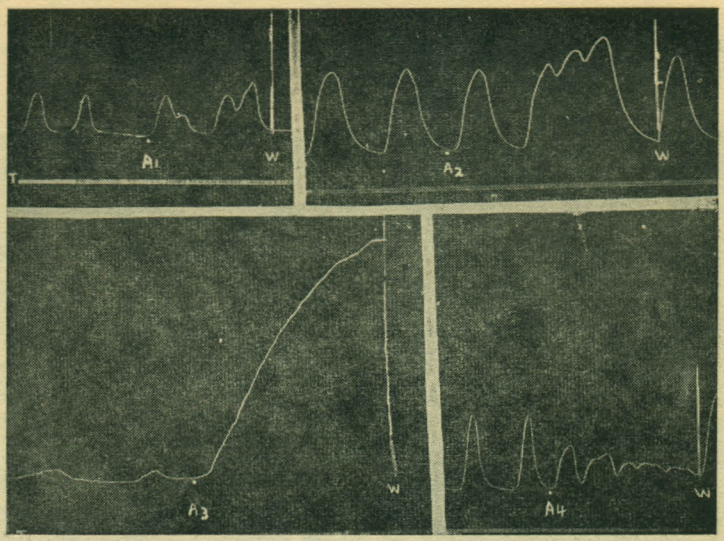


Fig. 1. Showing the effect of Compound A on guineaping uterus. At A_1, A_2, A_3, and A_4 0.2, 10, 20 and 100 μg/ml. respectively of Compound A was given, W, indicates wash.

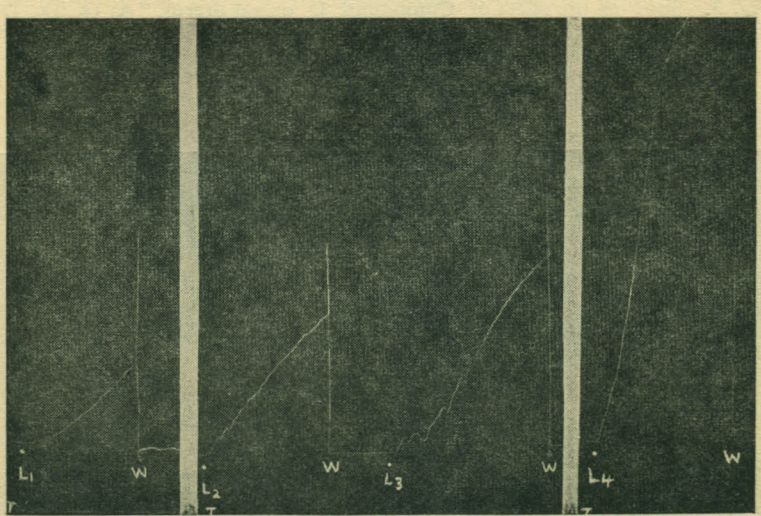


Fig. 2. Showing the effect of Lignocaine on guineapig uterus. At L_1, L_2, L_3 and L_4, 0.2, 20, 100 and 200 μg/ml respectively of lignocaine was given, W, indicate wash.

of uterine contraction but accelarated the rhythmicity (Fig. 3) Larger doses however, caused further inhibition of uterine contractions. Compound E and Lignocaine caused stimulation of uterine rhythmicity and tone (Fig. 4).

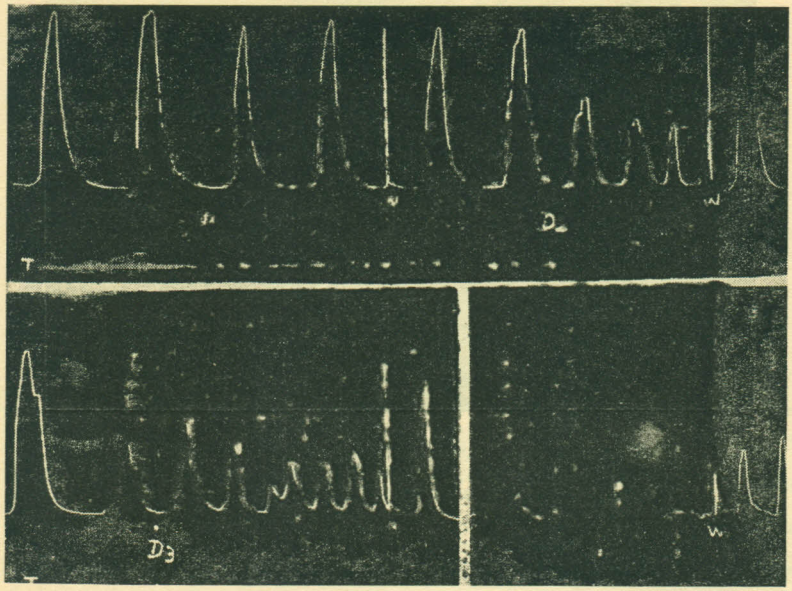


Fig. 3. Showing the effect of Compound D on rat uterus. At D_1, D_2, D_3 and D_4, 2, 10, 20 and 100 μg/ml respectively of Compound D was given, W, indicates wash.

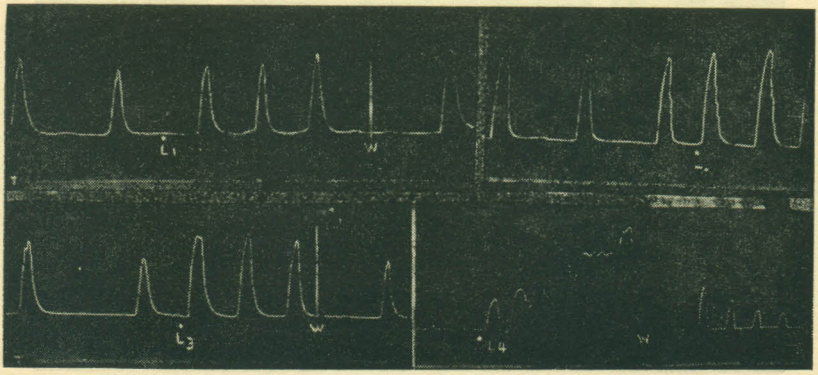


Fig. 4. Showing the effect of Lignocaine on rat uterus. At L_1, L_2, L_3 and L_4 0.2, 10, 20 and 200 μg/ml. respectively of Lignocaine was given, W, indicates wash.

DISCUSSION

The present study has shown that Lignocaine and its 6 analogues produce stimulant (oxytocic) action on the isolated uterii of guineapig and rat. The effects however, differ quantitatively and qualitatively in the two species of animals used. Guineapig uterii were generally found more sensitive to the stimulant effect of these local anaesthetics than those of rat, showing thereby a species variation. In an earlier study we (6) have shown that some of the analogues of Lignocaine tested for their local anaesthetic activity were many times more potent than the parent compound. We have also shown that they have in general spasmolytic activity on the smooth muscles such as intestine of rabbit, tracheal chain of guineapig, aortic strip of rabbit *etc* (3). A correlation of local anaesthetic activity and spasmolytic property was demonstrated. The effect of Lignocaine and its analogues on the uterine muscle is thus entirely independent of its action on other smooth muscles and there also does not seem to be any relationship between the local anaesthetic potency and the oxytocic action. Thus the Compounds F and C which were found to be most potent local anaesthetics and also spasmolytics, were found not much effective as oxytocic agents. It is not possible to correlate the chemical structure of these compounds with their stimulant (oxytocic) properties, mainly because the series is small.

SUMMARY

Lignocaine (Xylocaine) and some of its recently synthesized analogues were investigated for their oxytocic effect on the isolated uterii of guineapig and rat. Most of the compounds tested were found to possess powerful stimulant effect on the guineapig uterii but Lignocaine and Compound B were found most potent in this respect. The stimulant effect could not be seen with all the compounds on rat uterus except Lignocaine and compound E. There was no correlation between the stimulant properties of these compounds and their pharmacological actions on smooth muscle and local anaesthetic activity.

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