

EFFECTS OF ADRENERGIC NEURONE BLOCKING AGENTS ON GUINEA PIG ILEUM

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Sharma and Rajapurkar (3) while studying the actions of adrenergic neurone blocking drugs on intestinal peristalsis observed that bretylium and xylocholine in bigger doses produced a stimulant response on the longitudinal movements of guinea pig ileum where as guanethidine had no stimulant action (unreported observations). Those observations are in consonance with the observations of Boura and Green (2), who however, did not investigate the stimulant response further. We Studied the response in detail in this laboratory and have some interesting observations which are reported in this paper.

LONGITUDINAL MOVEMENTS OF GUINEA-PIG-ILEUM MATERIALS AND METHODS:

Method followed was that described by Burn(1). Guinea pigs were given a blow on the head and killed by cutting the carotid arteries. Ileum was removed and lumen washed with Krebs Hansle's solution. Two inch piece was mounted in an isolated organ bath containing above solution which was continuously bubbled with a mixture of 95% of O_2 and 5% CO_2 . Contractions were recorded by a frontal writing lever on a smoked drum. The effect of adrenergic neurone blocking agents was studied for 30 seconds after putting the drug in the bath in appropriate concentration. Responses are recorded after every two minutes. When atropine, ganglion blocking agent, antihistaminic or methisergide were used, they were kept in the bath in appropriate concentrations for two minutes and then the response of adrenergic neuronal blocking agent recorded for 30 seconds as described above

Drugs : Doses of the drugs are expressed in terms of their respective salts. Xylocholine bromide, bretylium tosylate, guanethidine sulphate, acetylcholine chloride, atropine sulphate, histamine acid phosphate, mepyramine maleate, 5 hydroxytryptamine creatine sulphate, methisergide, nicotine acid tartrate, pentolinium tartrate.

Results :

Xylocholine and bretylium caused contractions of the ileum in the concentration ranging from 25-400 $\mu g/ml$ and 50 to 800 $\mu g/ml$. respectively (Fig. 1 and 2). The contraction of intestine started immediately and the intestine relaxed after wash with normal Kreb's solution. Responses of xylocholine could be taken every two minutes but that of bretylium were taken every five minutes because if taken every two minutes bretylium showed tachyphylaxis. (Fig. 3)

Responses of xylocholine were not blocked by atropine (1 $\mu g/ml$), pentolinium (50 $\mu g/ml$), mepyramine (50 $\mu g/ml$) or methisergide (1 $\mu g/ml$) (Fig. 4, 5, 6 & 7). Responses of bretylium were blocked by atropine (1 $\mu g/ml$) and pentotinium 50 $\mu g/ml$, but not by mepyramine 50 $\mu g/ml$. methisergide (Fig. 4, 5, 6 & 7). Guanethidine did not cause contraction of intestine upto 1 mg/ml.

Discussion :

It is very interesting to observe that xylocholine and bretylium caused contraction of the intestine while guanethidine did not do so. Our results agree with those of Boura and Green(2). The action of xylocholine on the intestine is not blocked by atropine, pentolinium, mepyramine or methisergide. This indicates that the action of xylocholine is directly on the

plain muscle of the intestine and is not due to either ganglionic stimulation or due to liberation of acetylcholine, histamine or 5-hydroxytryptamine. Xylocholine also did not show tachyphylaxis. This is also in favour of its direct action on the plain muscle.

Bretlyium on the other hand caused contraction of the intestine by causing stimulation of the intramural ganglia because its action is blocked by pentolinium. The action of bretlyium is also blocked by atropine showing thereby that the stimulation of ganglia by bretlyium leads to liberation of acetylcholine the action of which is blocked by atropine.

Bretlyium also shows tachyphylaxis which is again in the favour of its ganglionic stimulant action.

The response of bretlyium is not blocked by mephyrumine or methisergide which indicate that the action is not due to liberation of histamine or 5-hydroxytryptamine, guanethidine does not cause contraction of the intestine.

The study of the action of these drugs with their mechanism of action on the intestine may help in identification among these three drugs.

It is also suggested that because of the lack of smooth muscle and ganglion stimulant action in guanethidine, it should be preferred as adrenergic neurone blocking agent clinically as well as in research over bretlyium and xylocholine.

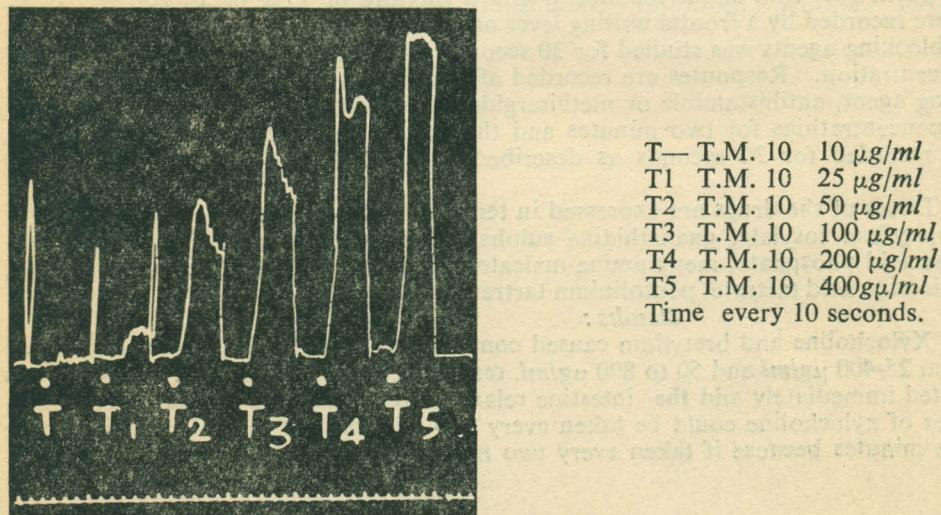


Fig. 1 : Showing the graded responses of T.M. 10 (Xylocholine) on guinea-pig-ileum.

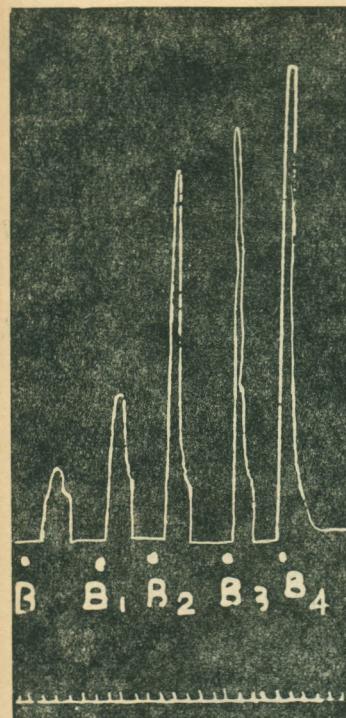
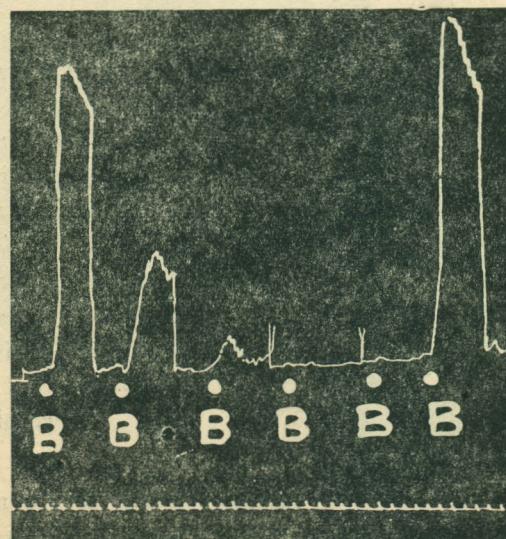


Fig. 2 : Showing the graded responses of Bretylium on guinea-pig-ileum

B	Bretylium	50	$\mu\text{g}/\text{ml}$
B1	Bretylium	100	$\mu\text{g}/\text{ml}$
B2	Bretylium	200	$\mu\text{g}/\text{ml}$
B3	Bretylium	400	$\mu\text{g}/\text{ml}$
B4	Bretylium	800	$\mu\text{g}/\text{ml}$

Time every 10 seconds.



B- Bretylium $400 \mu\text{g}/\text{ml}$. every two minutes. Last response is after 15 minutes

Time every 10 seconds

Fig. 3 : Showing tachyphylaxis by Bretylium on guinea-pig-ileum.

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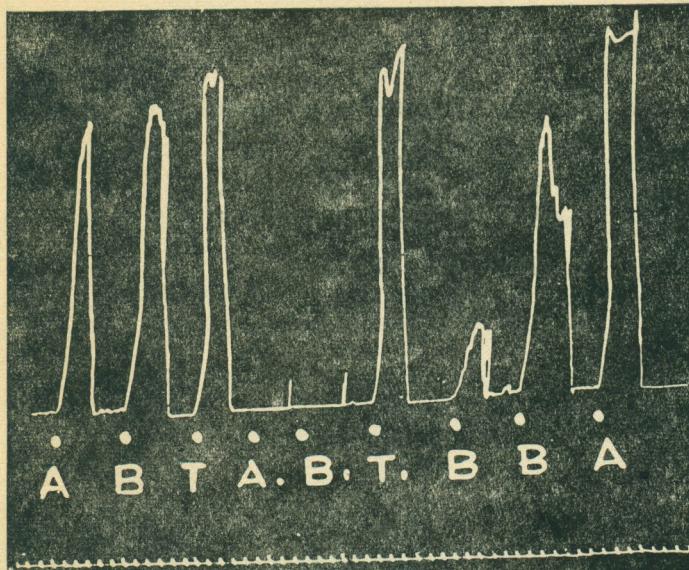
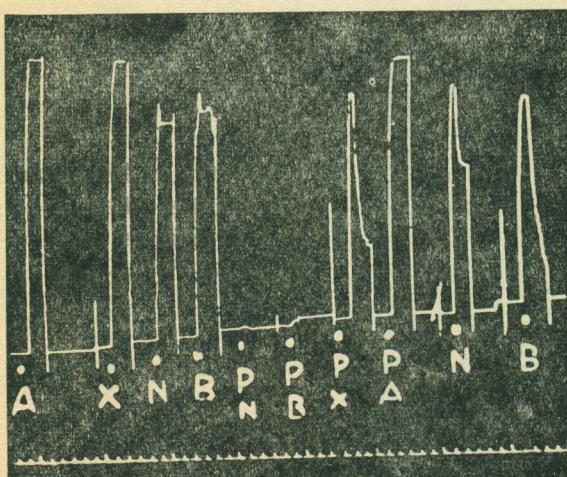


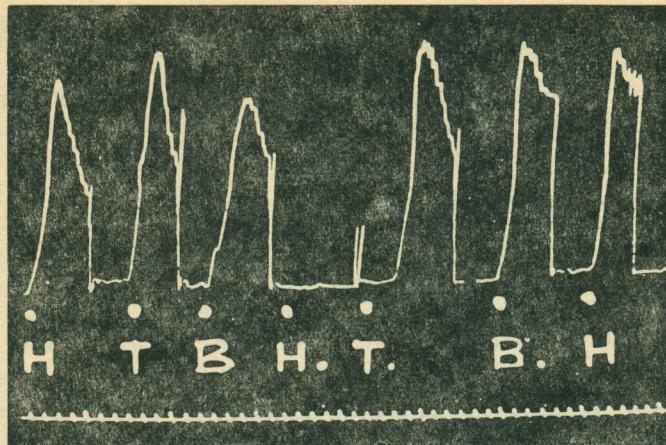
Fig. 4 : Showing the effect of atropine on the responses of Bretylium and T.M. 10 (Xylocholine) on guinea-pig ileum.



A—Acetylcholine 0.1 $\mu\text{g}/\text{ml}$
 X—T.M. 10 200 $\mu\text{g}/\text{ml}$
 N—Nicotine 5 $\mu\text{g}/\text{ml}$.
 B—Bretylium 400 $\mu\text{g}/\text{ml}$
 PN—Nicotine 5 $\mu\text{g}/\text{ml}$. in presence of
 Pentolinium 50 $\mu\text{g}/\text{ml}$
 PB—Bretylium 400 $\mu\text{g}/\text{ml}$. in presence of
 Pentolinium 50 $\mu\text{g}/\text{ml}$
 PX—10 $\mu\text{g}/\text{ml}$. in presence of Pentol
 inium 50 $\mu\text{g}/\text{ml}$
 PA—Acetylcholine 0.1 in presence of
 Pentolinium 50 $\mu\text{g}/\text{ml}$

Time every 10 seconds.

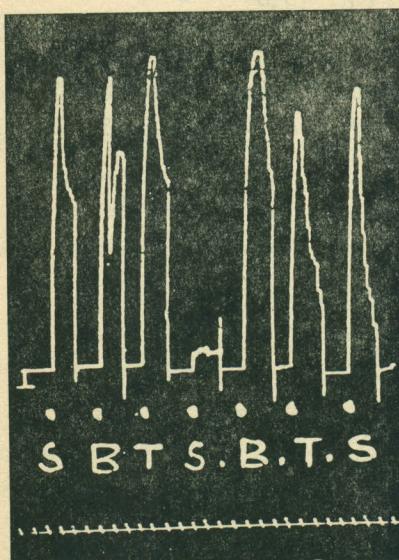
Fig. 5 : Showing the effect of Pentolinium on the response of Bretylium and T.M. 10 (Xylocholine) on guinea-pig ileum.



- H. Histamine 0.1 $\mu\text{g}/\text{ml}$
T. T.M. 10 200 $\mu\text{g}/\text{ml}$
B. Bretylium 400 $\mu\text{g}/\text{ml}$
H. Histamine 0.1 $\mu\text{g}/\text{ml}$. in presence of Mepyramine 50 $\mu\text{g}/\text{ml}$
T. T.M. 10 200 $\mu\text{g}/\text{ml}$. in presence of Mepyramine 50 $\mu\text{g}/\text{ml}$
B. Bretylium 400 $\mu\text{g}/\text{ml}$. in presence of mepyramine 50 $\mu\text{g}/\text{ml}$

Time every 10 seconds

Fig. 6 : Showing the effect of Mepyramine on the responses of Bretylium and T.M. 10 (Xylo-choline) on guinea-pig ileum.



- S. Serotonin (5 HT) 1 $\mu\text{g}/\text{ml}$
B. Bretylium 400 $\mu\text{g}/\text{ml}$
T. T.M. 10, 200 $\mu\text{g}/\text{ml}$
S. Serotonin 1 $\mu\text{g}/\text{ml}$. in presence of Methisergide 1 $\mu\text{g}/\text{ml}$
B. Bretylium 400 $\mu\text{g}/\text{ml}$. in presence of Methisergide 1 $\mu\text{g}/\text{ml}$
T. T.M. 10 200 $\mu\text{g}/\text{ml}$. in presence of Methisergide 1 $\mu\text{g}/\text{ml}$

Time every 10 Seconds.

Fig. 7 : Showing the effect of Methisergide on the responses of Bretylium and T.M. 10 (Xylo-choline) on guinea-pig ileum.

SUMMARY

1. Action of Xlocholine, Bretylium and Guanethidine is studied on guinea-pig-ileum.
2. Xylocholine stimulated intestine by its direct action on the plain muscle, Bretylium did so by stimulating the intramural ganglia while Guanethidine did not cause contraction of intestine.
3. The study of the action of these drugs with their mechanism of action on the intestine may help in identification among these three drugs.

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