SPASMOLYTIC ACTIVITY OF TWO SYNTHETIC ANILIDE LOCAL ANAESTHETICS

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Summary: Two basic anilides EA-7 and EA-8 were investigated for their antispasmodic activity against a variety of spasmogens on different tissues from different species of animals and comparison was made with lignocaine. EA-8 was found to be the most potent in this respect, followed by EA-7 and lignocaine. The antispasmodic potency does not correspond to their local anaesthetic potency. This suggests a direct depressant effect on tissues.

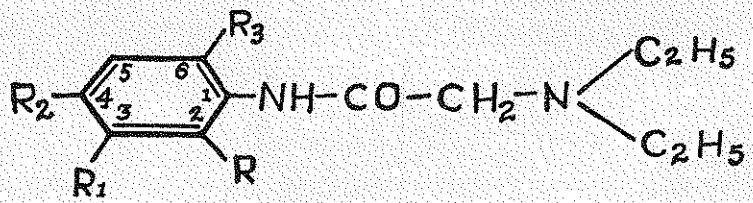
Key words: spasmolytic activity

INTRODUCTION

Local anaesthetics have been reported extensively to possess anticonvulsant, antiarrhythmic, neuromuscular blocking and antimicrobial properties (6, 8, 9, 10, 11). Besides, as a group they also possess spasmolytic activity and depress the contractions of the smooth muscle strips of isolated intestine. Further, it is reported that there is little correlation between the anaesthetic potency and antispasmodic efficacy, and this spasmolytic action, which can antagonise the spasm produced by a variety of chemical agents, seems to be caused by a direct depression of smooth muscle (5). Astron (1) has reported antagonism by certain local anaesthetics including lignocaine of adrenaline, noradrenaline and histamine induced contractions of the isolated rabbit aortic strip. He observed that antagonism was nonspecific and was independent of the local anaesthetic potency. However, Jindal and Patel (7), have observed a close parallelism between local anaesthetic activity and musculotropic action of some compounds.

A series of synthetic basic anilides have been reported by Grewal and Singh (4) to possess significant local anaesthetic activity. Out of these compounds code Nos. EA-7 and EA-8 were found to be quite potent. These bear structural resemblance to lignocaine as shown in Table I.

TABLE I: Chemical structure of the local anaesthetics.



Compound	*R*	*R*$_1$	*R*$_2$	*R*$_3$
Lignocaine	CH_3	H	H	CH_3
EA-7	H	C_2H_5	H	H
EA-8	H	H	C_2H_5	H

Therefore it was thought worthwhile to investigate antispasmodic activity of EA-7 and EA-8, on different tissues obtained from different animals, against various spasmogens. Besides, these compounds were also tested on isolated rabbit ileum for their effect on tone and force of normal contraction. An attempt has been made to elucidate the mechanism of action and possible relationship to local anaesthetic potency.

MATERIALS AND METHODS

Isolated pieces of ileum of rat, rabbit and guinea pig were suspended in 20 *ml* bath, containing appropriate physiological solution aerated with oxygen. The effects of local anaesthetics were observed against spasmogens acetylcholine, histamine and barium chloride. The local anaesthetic was allowed to remain in the bath for 60 seconds, before recording contraction with the spasmogen for 30 seconds. The effect of local anaesthetic was also observed on the normal pendular movements of the rabbit ileum in different concentrations ranging between 5-160 *mcg/ml* of the bath fluid.

Rabbit aortic strip was prepared by the method described by Furchgott and Bhadrakom (3). It was mounted in a 10 *ml* bath at 37°C, containing Kreb's solution, aerated with oxygen. Adrenaline and noradrenaline were used as spasmogens in concentrations of 1 *mcg/ml*, of the bath fluid. The tissue was treated with the local anaesthetic for 1 minute and without washing, effect of spasmogen was recorded for 2 minutes.

Method described by Castillo and De-Beer (2) was followed for preparing guinea pig tracheal chain, which was mounted in a 10 *ml* bath containing Kreb's solution at 37°C, aerated with oxygen. Histamine and acetylcholine in respective concentrations of 1 and 2 *mcg/ml*, were used to induce the contractions.

The local anaesthetic was allowed to act for 3 minutes, and without washing, the spasmogen was added and the effect recorded for 5 minutes.

The concentrations of spasmogens mentioned in Table II were strictly followed and the preparations showing inadequate response to these were discarded. The doses of local anaesthetics were selected in a logarithmic order. In all experiments, spasmolytic ED_{50} of lignocaine and EA-7 or EA-8 were worked out by plotting the log doses (abscissa) against percentage inhibiiton (ordinate), on the same tissue using the same spasmogen.

RESULTS

The three local anaesthetics viz. EA-7, EA-8 and lignocaine exhibit antispasmodic action against various spasmogens used in this study, the degree of inhibition being directly proportional to their concentration. The comprehensive results are depicted in Table II.

On isolated intestinal preparations, EA-8 is the most potent antispasmodic against various agonists except against acetylcholine on rat ileum and histamine on guinea pig ileum where

TABLE II: Relative potency of local anaesthetics in terms of their spasmolytic activity.

Spasmogens	*Conc/ml.*	*Tissue*	*Relative potency*		
			Lignocaine	*EA-7*	*EA-8*
1. ACH hydrochloride	0.1 µg	Rabbit ileum	I	2.5	3.2
	0.1 µg	Rat ileum	I	3.5	2.3
	0.1 µg	G.P. ileum	I	4	9.1
	2.0 µg	G.P. tracheal chain	I	2.9	3.1
2. Barium chloride	0.1 *mg*	Rabbit ileum	I	2.1	5.3
	0.1 *mg*	Rat ileum	I	2	4
3. Histamine acid phosphate	0.1 µg	G.P. iluem	I	7.7	3.7
	1.0 µg	G.P. tracheal chain	I	8	2.4
4. Adrenaline chloride	1.0 µg	Rabbit aortic strip	I	5.9	7.9
5. Noradrenaline bitrate	1.0 µg	Rabbit aortic strip	I	3.3	4.3

Relative potency = Spasmolytic ED_{50} of lignocaine/spasmolytic ED_{50} of EA-7 or EA-8.

EA-7 was found to be more potent. Both local anaesthetics also reduced considerably the tone and force of spontaneous contractions of rabbit ileum. EA-7 in concentrations of 40 *mcg/ml* produces the same degree of depression as 160 *mcg/ml* of lignocaine (Fig. 1).

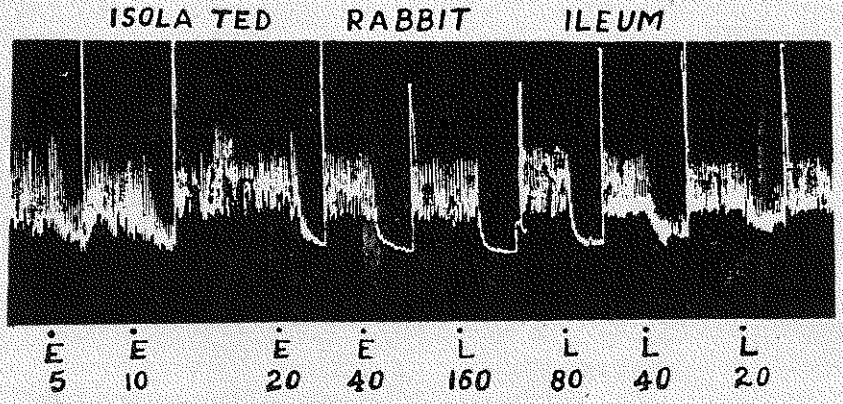


Fig. 1: Effect of EA-7 (E) and Lignocaine (L) on isolated rabbit ileum. Doses are expressed in *mcg/ml* of bath fluid. The relaxant activity of 40 *mcg/ml* EA-7 approaches that of 160 *mcg/ml* of Lignocaine.

The two local anaesthetics, like lignocaine, effectively antagonised the contraction of rabbit aortic strip, induced by adrenaline and noradrenaline, EA-8 being the most potent. As shown in Fig. 2, EA-8 in concentrations of 100 *mcg* and 300 *mcg/ml* caused inhibition of noradrenaline (1 *mcg/ml*) induced contractions by about 40% and 90%, respectively, where EA-7 and lignocaine in similar concentrations caused only 36% and 80%, 13% and 30% inhibition, respectively. They also inhibited acetylcholine and histamine induced contractions on guinea pig tracheal chain. EA-7 was relatively more potent than EA-8 against histamine,

where as against acetylcholine their potency was almost the same. EA-7 in concentration of 50 and 100 *mcg/ml* inhibited histamine contraction by 50% and 80% where as in similar concentrations lignocaine caused only 25% and 40%, respectively (Fig. 3).

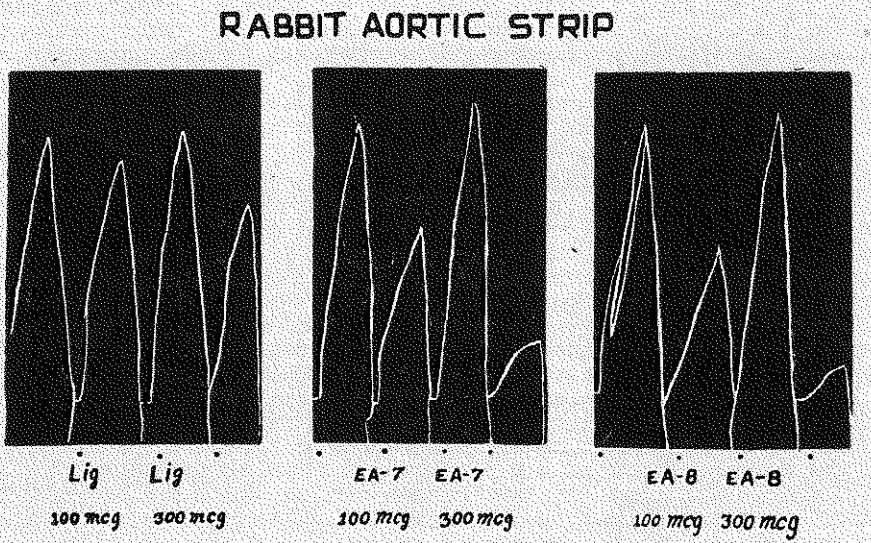


Fig. 2: Comparison of antispasmodic action of EA-7, EA-8 and Lignocaine on rabbit aortic strip preparation. Doses are expressed in *mcg/ml* of bath fluid. All contractions are due to nor-adrenaline 1 *mcg/ml*. Both EA-8 & EA-7 are more potent than Lignocaine.

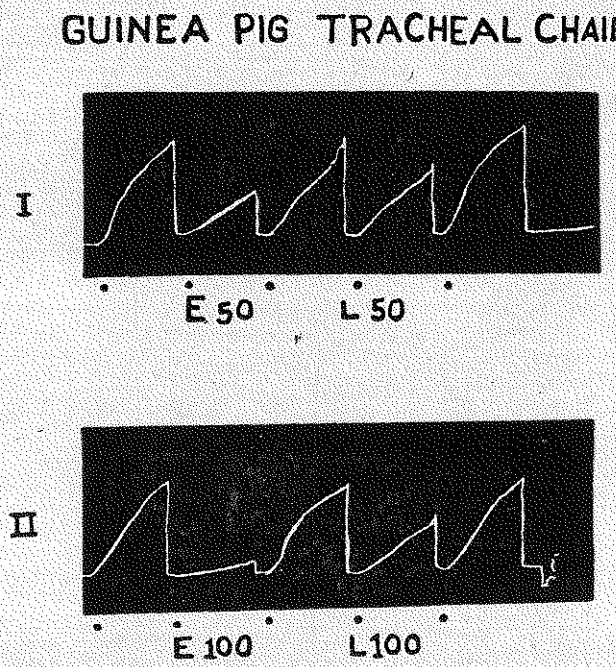


Fig. 3: Comparison of antispasmodic effect of EA-7 (E) and Lignocaine (L) on guinea pig tracheal chain. All doses are expressed in *mcg/ml* of bath fluid. Contractions were induced by Histamine 1 *mcg/ml*. Similar concentrations of EA-7 produce greater degree of effect than Lignocaine.

DISCUSSION

The two substituted anilide local anaesthetics EA-7 and EA-8 produced significant antispasmodic activity, being more potent than the reference drug lignocaine. EA-8 was more potent than EA-7 with only a few exceptions viz. against acetylcholine on rat ileum and against histamine on guinea pig ileum and tracheal chain. In no instance lignocaine reached the potency of either EA-7 or EA-8. But local anaesthetic potency was in reverse order i.e. lignocaine being the most potent followed by EA-7 and EA-8 (4). It is evident that the antispasmodic potency and therefore the action, is independent of the local anaesthetic potency. It seems likely that these compounds exert their effect due to a direct depression of smooth muscle and not because of their local anaesthetic action. Our findings with these two local anaesthetics are in agreement with some earlier reports (1,5). These compounds antagonise the contraction induced by a variety of chemical agents in different tissues obtained from various species of animals. This indicates that the spasmolytic activity is non-specific in nature and suggests a direct action on the muscle.

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