Beta Adrenergic Blocking Agents: Local Anaesthetic Activity, Comparison With Lignocaine

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The local anaesthetic activity of Propranolol has been well documented. In this study four Beta Blocking Agents have been tested to find out if these agents also have this property.Propranolol, Timolol, Atenolol and Labetalol were compared with the local anaesthesia produced by Lignocaine. The method employed was intra-dermal wheal injection, into the skin of the lower back of experimental rabbits. Propranolol and Labetalol produced significant local anaesthetic, whereas Timolol and Atenolol failed to achieve the same effect.
Key words: Beta adrenergic blocking agents, .local anaesthesia, lignocaine.

The membrane stabilising action of Beta receptor blocking drugs may manifest itself as local anaesthesia e.g. reduction in spike potential of isolated nerves, surface anaesthesia in the rabbit conjunctival sac, or infiltration anaesthesia, as demonstrated by the guinea pig wheal test.

Among the Beta Adrenergic Blocking Agents a few are known to have definite local anaesthetic effect. These members are Propranolol, Alprenolol, Oxprenolol, and Acebutolol. In this study attempt has been made to find out. if there is any local anaesthetic activity present in other members of the group of Beta Adrenergic Blocking Agents under investigation.

Material and methods

The experimental work was performed in the Laboratary of Experimental Pharmacology, Allama Iqbal Medical College, Lahore. Rabbits were supplied by the animal house of the Post-Graduate Medical Institute, Lahore. Beta Adrenergic Blocking Agents were used in the pure powder form. These products were supplied by their respective manufacturing companies:

Propranolol (Inderal)- Imperial Chemical Industries, U.K.
Atenolol (Tenormin)- - do -
Timolol (Blocadren)- Merck, Sharp & Dhome, U.S.A.
Labetalol (Trandate)- Glaxo, Pakistan.

Adrenergic Blocking Agents under study were Propranolol, Timolol, Atenolol and Labetalol. Local anaesthetic activities of two doses of each of these Beta Adrenergic Blocking Agents and 2 doses of Lignocaine were compared by Intradermal wheal method as employed by Bülbring and Wajda[1] for studying the local anaesthetic activity in rabbits.

Intradermal injection

A sterile sharp Insulin syringe needle was used for each injection. The skin on the lower back of the rabbit was stretched taut by holding the animal with the hand placed around the abdomen and by pulling the skin with the thumb and fore-finger. The drug was injected in the same direction as that in which the skin was being held and the needle was inserted in the dermis. Considerable pressure was needed for this. The plunger of the syringe was withdrawn slightly, appearance of blood indicated that the needle had gone subcutaneous. In such a case, the needle was removed and the prick was tried again. The volume injected intra-cutaneously was 0.2 ml, it was enough to raise a wheal which was then outlined with a felt tipped pen. Four wheals were produced on the lower back of each animal.

To allow for variation in the sensitivity of different parts of the skin of back, and of different animals, two doses of the Beta Adrenergic Blocking Agents under study and two doses of Lignocaine were given in different doses. Details of injection of drugs are given in Table 1.

The doses employed in the experiments were as follows:

Lignocaine 500 µg/ml(S_1), 1 mg/ml (S_2)
Beta Adrenergic Blocking Agents 2.5 x 10^{-3} g/ml (T_1), 5 x 10^{-3} g/ml (T_2)

After the intracutaneous injection, sensitivity of the injected area was tested by pricking with a needle six times lightly, and, as a control, the skin as far away from it as possible. Six twitches could be recorded from the area serving as the control. The responses at the site of injection indicated the degree of anaesthesia, which was expressed as the number of negative responses out of the six pricks given i.e. failure to twitch 6/6, indicated maximum anaestheisa and 0/6 indicated no aneasthesia.

This stimulus was applied in a series of six tests on each test area at zero time and at intervals of 10 minutes for a 40 minutes period. A positive score was noted each time the animal did not respond.

The total score of each wheal was added up and expressed as the total number of negative responses out of the maximum possible thirty negative responses. Each Beta Adrenergic Blocking Agent was tested with the two doses, in different orders in four different animals. The total score at each site of injection is given in detail in Table1.

The mean of negative responses for each dose of each drug was calculated and it is presented in an abbreviated form in the Table2.

The local anaesthetic activity of each one of the Beta Adrenergic Blocking Agents under study has been compared individually with lignocaine. It is presented graphically as log dose/effect curves in Figure A.

Table:1 Sites of injection & the drugs injected on the lower back of rabbit

Animals	Right Upper wheal	Right Lower wheal	Left Upper wheal	Left Lower wheal
A	$Lignocaine_1$ (25)	$Lignocaine_2$ (22)	$Propranolol_1$ (28)	$Propranolol_2$ (30)
B	$Lignocaine_2$ (29)	$Propranolol_1$ (28)	$Propranolol_2$ (23)	$Lignocaine_1$ (21)
C	$Propranolol_1$ (30)	$Propranolol_2$ (28)	$Lignocaine_1$ (20)	$Lignocaine_2$ (26)
D	$Propranolol_2$ (30)	$Lignocaine_1$ (21)	$Lignocaine_2$ (28)	$Propranolol_1$ (30)
E	$Lignocaine_1$ (20)	$Lignocaine_2$ (23)	$Timolol_1$ (23)	$Timolol_2$ (23)
F	$Lignocaine_2$ (25)	$Timolol_1$ (7)	$Timolol_2$ (8)	$Lignocaine_1$ (25)
G	$Timolol_1$ (13)	$Timolol_2$ (14)	$Lignocaine_1$ (20)	$Lignocaine_2$ (26)
H	$Timolol_2$ (12)	$Lignocaine_1$ (19)	$Lignocaine_2$ (23)	$Timolol_1$ (19)
I	$Lignocaine_1$ (29)	$Lignocaine_2$ (26)	$Atenolol_1$ (17)	$Atenolol_2$ (16)
J	$Lignocaine_2$ (26)	$Atenolol_1$ (8)	$Atenolol_2$ (16)	$Lignocaine_1$ (18)
K	$Atenolol_1$ (8)	$Atenolol_2$ (9)	$Lignocaine_1$ (22)	$Lignocaine_2$ (23)
L	$Atenolol_2$ (20)	$Lignocaine_1$ (24)	$Lignocaine_2$ (23)	$Atenolol_1$ (21)
M	$Lignocaine_1$ (23)	$Lignocaine_2$ (25)	$Labetalol_1$ (27)	$Labetalol_2$ (30)
N	$Lignocaine_2$ (26)	$Labetalol_1$ (19)	$Labetalol_2$ (26)	$Lignocaine_1$ (30)
O	$Labetalol_1$ (29)	$Labetalol_2$ (23)	$Lignocaine_1$ (22)	$Lignocaine_2$ (26)
P	$Labetalol_2$ (29)	$Lignocaine_1$ (24)	$Lignocaine_2$ (24)	$Labetalol_1$ (28)

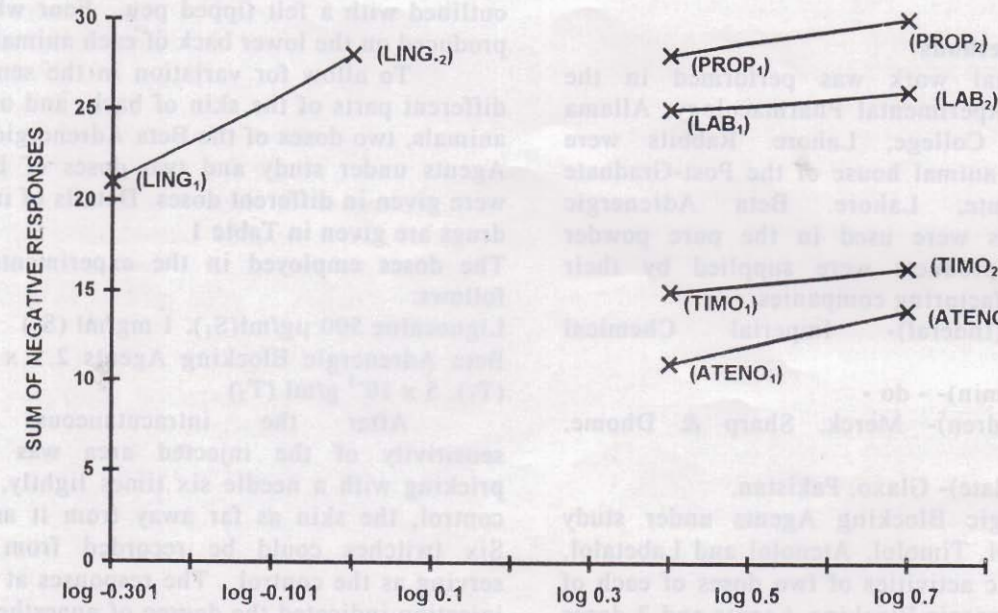

Fig A: A Comparison of the local anesthetic effect of beta adrenergic block agents and Lignocaine.

Table 2 Mean negative responses at each intra-cutaneous injection site

Control	S_1	S_2	TEST	T_1	T_2
Lignocaine	21.75 /30	26.25 /30	Propranolol	26/30	29/30
Lignocaine	21.00 /30	24.50 /30	Timolol	15.5/30	16.75/30
Lignocaine	23.50 /30	24.50 /30	Atenolol	13.5/30	15.25/30
Lignocaine	24.75 /30	25.25 /30	Labetalol	25.75/30	27/30

Total number of pricks given in each erea of injection = 30
The score written in front of each drug is the total number of negative responses out of the maximum possible 30 negative responses, at each site of injection.

Discussion

Local anesthetic action, also known as "Membrane-Stabilizing" action, is a prominent effect of several Beta Blockers. This action is the result of typical local anaesthetic like blockade of sodium channels and can be demonstrated in neurons, heart muscle, and skeletal muscle membrane[1].

In our study Propranolol and Labetalol have been demonstrated to have a local anaesthetic effect, almost equal to that of Lignocaine.Timolol and Atenolol did not produce significant local anaesthetic. Our results are in agreement with the study carried out on the local anaesthetic "quinidine like" activity of five Beta Blockers[2].

It was reported that Propranolol, Pronethalol and INPEA exhibit local anaesthetic activity when assessed by infiltration anaesthesia and by blocking of motor nerve endings. These agents also exhibited "Quinidine Like" activity and a close co-relation between local anaesthetic and Quinidine Like activities was suggested.

Besides, relative activities of Beta Blockers compared with Procaine as "Quinidine Like" agents: were similar to their potencies as local anaesthetic, when assessed by Intradermal Wheal method and as nerve blocking agents[2].

The concentration of Beta Blockers required to produce Beta Blockade are some 1000 times smaller than the concentration required to produce "Quinidine Like" action on atria and blockade on motor nerve endings[2].

Our results are further in agreement with the experimental data collected by S. Evan Glista[6] who has reported local anaesthetic and antidysrrthymic ($Ca\text{-}Cl_2$ induced) activities of Propranolol, Aplronolol and Metoprolol. He also reported no local anaesthetic activity of Atenolol, Practolol and Sotalol in a concentration as high as 6%. This again supported our results. The local anaesthetic like electrophysiological effect of Propranolol when given in high concentration have also been reported[8].

Doggrell-S.A. has suggested that the Membrane Stabilising activity of Beta Blockers could be relavent clinically[5]. Aquagenic Pruritis has been reported by Thomsen-K to responds to Propranolol[6]. In clinical trials Prolongation of pain threshhold time in healthy volunteers, caused by Propranolol has been reported [7].

The technique employed in our study is Intradermal Injection of Beta Blockers on Rabbit's skin which caused marked local anaesthetic. Propranolol has been injected sub cutaneously by Nakamura et.al[8] in conscious guinea pigs. This led to decrease in the vocallizing response to electric stimulation.

This experimental technique is quite similar to the method employed in our study. The results are also in agreement with the results of Propranolol induced anaesthesia.

In conclusion, our comparative study of four Beta Blockers shows significant local anaesthetic activity demonstrated by the two lipophillic agents namely Propranolol and Labetalol. Timolol and Atenolol failed to produce such activity. These results are in agreement with the report of special features of different Beta Blockers tabulated by Brain-B. Haffman in[1].

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