

## DEMONSTRATION OF DEPRESSANT EFFECT OF PROPRANOLOL AND ACEBUTOLOL ON THE CONTRACTILE RESPONSE OF RAT ISOLATED DIAPHRAGM WITH ELECTRICAL STIMULATION

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**Background:** Propranolol is a non-selective, while acebutolol is a cardioselective beta blocker. This study was designed to implore into the effect of nonselective and cardioselective beta blockers on the electrically stimulated contractile response of isolated diaphragm of rat. **Methods:** Study was conducted on male and female rats of albino variety, weighing 150-200 grams, in Jinnah Postgraduate Medical Centre Karachi. Diaphragmatic strips were prepared. Tissue was transferred to a tissue bath containing oxygenated Krebs solution kept at 32°C. One end of the strip was connected to the electrodes of an electric stimulator, while its other end was connected to a polygraph through a force displacement transducer. Normal recordings of the response of tissue to electrical stimulation was obtained. The response was observed with  $10^{-8}$  -  $10^{-3}$  M concentrations of propranolol and acebutolol separately and in series. Contractile response of the tissue was measured in millimeters. Arithmetic mean for each set of observation was determined. T test was performed and P value was determined from the t table. **Results:** Both propranolol and acebutolol produced significant depression of the contraction of rat isolated diaphragm as a result of electrical stimulation. **Conclusion:** Our study has shown that the depressant effect of beta adrenoceptor blocking drugs, perhaps, do not play important role in the etiology of respiratory distress produced by these drugs, because the depressant effect of both propranolol and acebutolol on diaphragm are only produced in high doses.

### INTRODUCTION

Propranolol is a non-selective, while acebutolol is a cardioselective beta blocker. Both of these beta adrenoceptor blockers produce bronchospasm, especially in persons suffering from bronchial asthma and chronic obstructive bronchopulmonary diseases. Relatively trivial asthma may become severe with the use of beta adrenoceptor blockers, especially B<sub>2</sub>-adrenoceptor blockers.<sup>1</sup> McDonald et al,<sup>2</sup> Besterman<sup>3</sup> and Bongrani et al,<sup>4</sup> by their experiments on animals and humans concluded that the bronchospasm induced by beta adrenoceptor blockers was due to the blockade of beta adrenoceptors on the smooth muscle of the lungs. On the other hand Maclogan and May by their experiments on the anaesthetized guinea-pigs concluded that bronchospasm induced by beta blockers was not related to their beta adrenoceptor blocking activity.<sup>5</sup>

Harry et al, in 1974 observed the effects of beta blockers on the isolated diaphragm of rat. They concluded that some of the beta blockers have significant depressant effect on the isolated diaphragm of rat, in which the contraction was induced by electrical stimulation.<sup>6</sup> Drazen et al, studied the effect of propranolol and isoprenaline on the isolated diaphragm of rat in response to the

maximal tetanic stimulation. They concluded that propranolol caused significant depression of the contractile response of the diaphragm, while isoprenaline had no such effect.<sup>7</sup> From the above review it is evident that diverse mechanisms may be involved in the respiratory distress produced by the beta blockers. This study was designed to explore into the effect of nonselective and cardioselective beta blockers on the electrically stimulated contractile response of isolated diaphragm of rat.

### MATERIAL AND METHODS

Study was conducted on male and female rats of albino variety, weighing 150-200 grams, in Jinnah Postgraduate Medical Centre Karachi. Rat was killed by a blow on the back of its head. Its diaphragm was then isolated and diaphragmatic strips were prepared according to the method of Drazen et al<sup>8</sup>. Tissue was transferred to a tissue bath containing oxygenated Krebs solution kept at 32°C. One end of the strip was connected to the electrodes of an electric stimulator, while its other end was connected to a polygraph (model PIB-7) through a force displacement transducer; d-tubocurarine was added to the tissue bath to prevent the neuromuscular stimulation of the tissue. Normal recordings of the response of tissue to electrical stimulation was obtained. The response was observed with  $10^{-8}$  -  $10^{-3}$

M concentrations of propranolol and acebutolol separately and in series. Contractile response of the tissue was measured in millimeters. Arithmetic mean for each set of observation was determined. T test was performed and P value was determined from the t table. Results were judged as significant when P value was less than 0.05.

## RESULTS

Propranolol caused depression of the contractile response to electrical stimulation by rat isolated diaphragm. The mean values of the magnitude of contraction produced by the isolated diaphragm before treatment with propranolol was 26±2.45, 23.4±1.76, 26.2±1.94, 27.7±3.43, 29.8±3.71 and 21.7±3.44 millimeters, while the mean values of the

magnitude of contraction after treatment with propranolol of 10<sup>-8</sup>M, 10<sup>-7</sup> M, 10<sup>-6</sup> M, 10<sup>-5</sup> M, 10<sup>-4</sup> M and 10<sup>-3</sup> M concentrations were 25.8±2.47, 22.3±2.42, 24.9±1.88, 27±3.42, 15.6±2.36 and 6.2±1.21 mm respectively. Acebutolol also caused depression of the isolated diaphragm to electrical stimulation. The mean values of the magnitude of contraction before treatment with acebutolol were 20.5±2.09, 24.5±2.2, 23.5±1.83, 16.9±2.15, 24.3±2.59 and 21.2±1.83 millimeters. While mean values of magnitude of contraction after treatment with acebutolol in concentrations of 10<sup>-8</sup>M, 10<sup>-7</sup> M, 10<sup>-6</sup> M, 10<sup>-5</sup> M, 10<sup>-4</sup> M and 10<sup>-3</sup> M were 19.9±2.22, 22.5±1.99, 21.8±2.60, 14.9±2.01, 17.1±1.71 and 7.9±0.97 millimeters respectively (Table-2).

**Table-1: Effect of electrical stimulation on isolated diaphragm of rat before and after treatment with Propranolol.**

Concentration of propranolol (Moles)		10 <sup>-3</sup>	10 <sup>-4</sup>	10 <sup>-5</sup>	10 <sup>-6</sup>	10 <sup>-7</sup>	10 <sup>-8</sup>
Normal Tissue	Amplitude of contraction (mm±S.E)	21.7±3.44	29.8±3.71	27.7±3.43	26.2±1.94	23.4±1.76	26.0±2.45
	Percent response	72.81(10)	100(10)	92.95(10)	87.91(10)	78.52(10)	87.24(10)
Tissue pretreated with propranolol	Amplitude of contraction (mm±S.E)	6.2±1.21	15.6±2.36	27.0±3.43	24.9±1.88	22.3±2.42	25.8±2.42
	Percent response	20.80(10)	52.34(10)	90.60(10)	83.55(10)	74.83(10)	86.57(10)
“P” Value		<0.05	<0.05	>0.05	>0.05	>0.05	>0.05

Figure in parenthesis indicate number of experiments performed.

S.E. means standard error.

P value less than 0.05 is significant.

**Table-2: Effect of electrical stimulation on rat isolated diaphragm before and after treatment with Acebutolol**

Concentration of acebutolol (Moles)		10 <sup>-3</sup>	10 <sup>-4</sup>	10 <sup>-5</sup>	10 <sup>-6</sup>	10 <sup>-7</sup>	10 <sup>-8</sup>
Normal Tissue	Amplitude of contraction (mm±S.E)	21.2±1.83	24.3±2.59	16.9±2.15	23.5±1.83	24.5±2.20	20.5±2.09
	Percent response	71.14(10)	81.54(10)	56.71(10)	78.85(10)	82.21(10)	68.79(10)
Tissue pretreated with acebutolol	Amplitude of contraction (mm±S.E)	7.9±0.97	17.1±1.71	14.9±2.01	21.8±2.60	22.5±1.9	19.9±2.22
	Percent response	26.51(10)	57.38(10)	50(10)	73.15(10)	75.5(10)	66.77(10)
“P” Value		<0.05	<0.05	>0.05	>0.05	>0.05	>0.05

Figure in parenthesis indicate number of experiments performed.

S.E. means standard error.

P value less than 0.05 is significant.

## DISCUSSION

Present study showed that both propranolol and acebutolol produced significant depression of contractile response of rat isolated diaphragmatic strip to electrical stimulation. But the depressant effect was observed only in high concentrations of the drugs. Propranolol is a nonselective blocker of the beta adrenoceptors, because it blocks both Beta 1 (B1) and Beta 2 (B2) adrenoceptors<sup>9</sup>. Acebutolol is a cardioselective beta adrenoceptor antagonist, because it mainly causes the blockade of beta1 (B1) adrenoceptors.<sup>10</sup> Administration of both propranolol and acebutolol can cause respiratory distress, especially in persons suffering from bronchial asthma and chronic obstructive bronchopulmonary disease.<sup>11</sup> Present study has shown that both propranolol and acebutolol show depressant effect on the diaphragm in high concentrations. Thus large doses of these drugs have to be used to produce depression of diaphragmatic contraction. Drazen et al<sup>7</sup> also demonstrated the depressant effect of propranolol on rat isolated diaphragm in response to its electrical stimulation. They also observed this effect at high concentrations of propranolol. They concluded that the depressant effect of propranolol on the rat isolated diaphragm was not related to its beta adrenoceptor blocking activity, but was due to membrane stabilizing effect of the drug. The results of the present study have shown that the depressant effect of beta adrenoceptor blocking drugs, perhaps,

do not play important role in the etiology of respiratory distress produced by these drugs. Because the depressant effect of both propranolol and acebutolol on diaphragm are only produced in high doses.

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