$$\mathbf{S} = \frac{1}{(n-p)}\left[\mathbf{Z}-\mathbf{R}\right]$$

The matrix B can be written in the form $\mathbf{b}_1 \ldots \mathbf{b}_p$ where $\mathbf{b}_i$ is the column vector of partial regression coefficients of all the response variables on x_i, the i-th regressor. The variance-covariance matrix of $\mathbf{b}_i$ is $\mathbf{V}_i = x^{ii}\mathbf{S}$, where x^{ii} is the element in the i-th row and column of $\mathbf{X}^{-1}$. Then we have $T_i^2 = \mathbf{b}_i'\mathbf{V}^{-1}\mathbf{b}_i$, and the significance of the regression can be tested by taking the quantity $\frac{(n-q+1)\,T^2}{nq}$ as a variance ratio with q and $(n-q+1)$ DF

If none of the regressors is found to be significant, then no regression adjustments are necessary. If the regressors $x_1 \ldots x_s$ $(s \leqq p)$ are significant, the correction of the test of significance for any contrast between the treatment means is made as follows:

Let $\bar{\mathbf{x}}$ be the $k \times s$ (assuming k treatment groups) matrix of means of the significant regressors, let $\bar{\mathbf{z}}$ be the $k \times q$ matrix of means of the response variables, let $\mathbf{U}$ be the variance-covariance matrix of the significant regressors ($\mathbf{U}$ is derived by eliminating from $\mathbf{X}$ any rows and columns corresponding to non-significant regressors, and dividing the resultant $s \times s$ matrix by n) and let $\boldsymbol{\theta}'$ be a *row* vector of factorial coefficients corresponding to any orthogonal contrast among the treatment means. Now let $\mathbf{d}' = \boldsymbol{\theta}'\bar{\mathbf{z}}$ be the row vector of differences for the contrast in question among the response variables, and let $\boldsymbol{\delta}' = \boldsymbol{\theta}'\bar{\mathbf{x}}$ be the corresponding vector for the regressors. Define the quantities

$$\text{LJ}_0 = \boldsymbol{\delta}'\mathbf{U}^{-1}\boldsymbol{\delta},\ \text{LJ} = \mathbf{d}'\mathbf{S}^{-1}\mathbf{d},\quad \text{f} = \frac{1}{\sum_i \frac{\theta_i}{n_i} + \text{LJ}_0}$$

then $T^2 = f\text{LJ}$, and the T^2 can be tested as a variance ratio with q and $(n-q+1)$ DF as described above.

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Effect of five β-adrenoceptor antagonists on the effects of isoprenaline and acetylcholine on human isolated smooth muscle

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The effects of propranolol, practolol, alprenolol, oxprenolol and prinodolol (LB46) were studied on the responses to isoprenaline and acetylcholine of human isolated smooth muscle. The tissues were obtained from operation specimens and were prepared as previously described (Coupar & Turner, 1969). Equilibrium pA_2 values were determined by the method of Schild (1947). pA_2 determinations at 2 min were carried out according to Lockett & Bartlett (1956). A time course for each antagonist

against acetylcholine showed that the maximum antagonism was reached after 2 minutes.

The results are shown in Table 1. The antagonism of all five compounds against isoprenaline was competitive over the concentration range tested (10 ng–250 ng/ml), while that against acetylcholine was non-competitive. The β-adrenoceptor antagonists were approximately 1,000 times less active against acetylcholine than isoprenaline. The relatively low pA_2 value for practolol v isoprenaline on bronchus, which has a predominantly β_2 receptor population (Lands, Arnold, McAuliff, Luduena & Brown, 1967), indicates that this antagonist is more specific for β_1 than β_2 receptors.

TABLE 1. *pA_2 values for five β-adrenoceptor antagonists against isoprenaline and acetylcholine*

Antagonist	Agonist: Isoprenaline Tissue		pA_2	Range	Acetylcholine Tissue		pA_2	Range
Propranolol	Bronchus (C)	(2)	6·65	(6·6–6·7)	Ileum (C)	(1)	4·13	
	*Colon (L)	(2)	6·98	(6·89–7·07)	Appendix (L)	(1)	4·08	
	*Stomach (L)	(1)	7·10		Colon (L)	(1)	4·18	
Alprenolol	*Colon (L)	(3)	6·89	(6·83–6·97)	Stomach (L)	(1)	3·91	
					Jejunum (L)	(1)	3·92	
					Appendix (L)	(1)	3·98	
Practolol	Bronchus (C)	(1)	4·20		Stomach (L)	(2)	3·50	(3·4–3·6)
	*Colon (L)	(3)	6·37	(6·3–6·5)	Ileum (L)	(1)	3·45	
Oxprenolol	Bronchus (C)	(1)	6·97		Stomach (L)	(2)	3·46	(3·41–3·51)
	*Colon (L)	(2)	7·25	(7·23–7·27)	Rectum (L)	(1)	3·50	
Prinodolol	Bronchus (C)	(2)	6·70	(6·6–6·8)	Ileum (L)	(1)	4·30	
	*Colon (L)	(2)	7·05	(6·9–7·2)	Ileum (C)	(1)	4·40	
	*Stomach (L)	(1)	7·20		Appendix (L)	(1)	4·22	

* Equilibrium pA_2 determinations. Numbers in brackets indicate number of experiments. (L) Longitudinal muscle; (C) circular muscle.

On strips of detrusor bladder neck muscle and of stomach, which responded to acetylcholine at 10 ng/ml, oxprenolol caused a direct contraction in concentrations of 10 μg/ml and above, which could be antagonized by atropine. This suggested that oxprenolol had some anticholinesterase action which was, therefore, measured by a colourimetric method for determining red blood cell cholinesterase activity in whole blood (Fleisher & Pope, 1954). The activity of oxprenolol was compared with eserine and propranolol. The mean concentration of eserine to inhibit the cholinesterase activity by 50% (ID50), was $2{\cdot}63\times10^{-10}$M ($n=6$) compared with $2{\cdot}75\times10^{-4}$M for oxprenolol. Propranolol at $7{\cdot}4\times10^{-4}$M caused only 12% inhibition. Therefore, oxprenolol is a weak cholinesterase inhibitor about 10^6 less potent than eserine.

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