Problems associated with the statistical analysis of drug interactions

B. J. JONES, D. J. ROBERTS and B. D. TOLMAN, *Department of Pharmacology, School of Pharmacy, Park Road, Portsmouth, Hampshire*

Investigations into the effects of one drug on the pharmacological properties of another are often complicated by the fact that both drugs may influence the parameter studied. In such cases this must be taken into account in the statistical analysis of the data.

We have met this problem while comparing the effects of a variety of drugs on the hypokinesia induced in mice by intraperitoneal injections of tetrabenazine and intracerebroventricular injections of noradnamine hydrochloride.

Motor activity is at the best of times an extremely variable parameter, but the use of large numbers of observations coupled with a powerful statistical technique has enabled us to tackle the problem of analysing drug interactions with fair success. We have used a factorial design in our experiments and the data have been analysed using the analysis of variance (Kinnard & Watzman, 1966).

For our purposes a programme has been written (by B.D.T.) for an Elliott 803B computer which allows analysis of the data without transformation or in one of five (x^{-1}, $x^{-\frac{1}{2}}$, x^{0}, $x^{\frac{1}{2}}$, x^{2}) transformations (Tukey, 1957).

The programme additionally includes tests for non-additivity and non-homogeneity of variance. The three basic assumptions of additivity, homogeneity of variance and normality underlying the analysis of variance (Snedecor, 1956) have been found to be most consistently satisfied by the use of the logarithmic transformation.

Details of the programme will be available and the method of its application and interpretation will be presented using our own experimental data.

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Relative potencies of sympathetic amines in human smooth muscle

I. M. COUPAR and P. TURNER, *Division of Clinical Pharmacology, Medical Professorial Unit, St. Bartholomew's Hospital, London, E.C.*1

The classification of α- and β-adrenoreceptive receptors is based on: (*a*) the order of potency of sympathomimetic amines in evoking these responses, and (*b*) the ability of adrenergic antagonists to block these responses. Although Bennett & Whitney (1966) have shown the existence of α- and β- inhibitory receptors in human gastrointestinal tract by the use of α- and β-receptor antagonists, the use of order of potency as a criterion for classification in human tissue has not received much attention.

The order of potency of adrenaline, isoprenaline and phenylephrine relative to noradrenaline (1·00) in human smooth muscle from various tissues has therefore been studied. Fresh surgical specimens were dissected free of superfluous tissue and suspended in an organ bath at 37° C. In all experiments the Krebs bicarbonate solution included cocaine HCl (5 μg/ml.) to block the amine uptake mechanism of the sympathetic nerve terminals, propranolol HCl (0·5 μg/ml.) to block β-adrenoreceptive receptors (except in artery and vein), and for ileum, colon and rectum

TABLE 1. *Potencies of adrenaline (A), isoprenaline (ISO), and phenylephrine (PE), relative to noradrenaline (N) as free bases on a number of human tissues containing smooth muscle*

Tissue		Number of specimens	Type of response	Mean relative potencies A	N	PE	ISO
Vein	Saphenous circular muscle	3	Contraction	4	1	0·08	0·005
Artery	Popliteal circular muscle	1	Contraction	4	1	0·2	—
Oesophagus	Lower third circular muscle	1	Contraction	5	1	0·2	—
Stomach	Pyloric antrum longitudina muscle	4	Inhibition of acetylcholine induced contractions	>1	1	<1	≤1
Ileum	Longitudinal muscle	3	Relaxation	5	1	0·2	0·005
Colon	Longitudinal muscle	3	Relaxation	3	1	0·2	0·005
				3	1	—	0·04
				10	1	—	0·03
Rectum	Longitudinal muscle	3	Relaxation	3	1	0·1	0·003
				2	1	0·1	0·2
				4	1	—	0·1
Bladder	Detrusor muscle	1	Contraction	2	1	0·3	—

—, No response obtained in the concentrations used.

amechol (0·1 to 5 μg/ml.) to induce tone. Relative potencies were determined by the method of Furchgott (1967), the results being shown in Table 1.

In all tissues studied the order of potency was adrenaline, noradrenaline, phenylephrine followed by isoprenaline. In artery and vein the response to these sympathetic amines was contraction (excitation). In gastro-intestinal, smooth muscle the response was relaxation (or inhibition) apart from oesophagus, in which contraction (excitation) occurred. The order of potency obtained in these tissues indicates a significant α-adrenoceptive receptor population (Furchgott, 1967; Ahlquist, 1948).

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Effects of prostaglandin E_2 (PGE_2) on the output of histamine and acid in rat gastric secretion induced by pentagastrin or histamine

I. H. M. MAIN, *Department of Pharmacology, School of Pharmacy, University of London*

The relationship between the output of histamine and acid from the rat stomach has been studied *in vivo* during intravenous infusion of pentagastrin and histamine. The lumen of the stomach was perfused with 0·8% saline (0·2–0·5 ml./min) and samples of perfusate were collected at 15 min intervals. Acid content was estimated by titrating an aliquot of each sample with N/100 sodium hydroxide and the histamine content of the remainder was assayed on isolated superfused ileum from the guinea-pig.