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The effect of bronchodilators upon pulmonary resistance and compliance in the anaesthetized guinea-pig

Laboratory methods for the evaluation of bronchodilator drugs in animals almost invariably depend upon inhibition of an induced bronchospasm (Dixon & Brodie, 1903; Konzett & Rössler, 1940) and reflect changes in pulmonary compliance rather than resistance (Widdicombe, 1966). However, clinical assessments usually measure changes in ventilatory function such as forced expiratory volume, vital capacity or more recently, a change in pulmonary resistance (Comroe, 1965). This latter technique is the only clinical method directly applicable to laboratory animals. Pulmonary resistance and compliance changes have been used to show bronchoconstriction and bronchodilation in the conscious guinea-pig (Douglas, Dennis & others, 1972) but quantitative measurements of the actions of several bronchodilator drugs do not appear to have been made. Some such experiments are now reported.

Male albino guinea-pigs, 350–500 g, after overnight starving were anaesthetized by the intraperitoneal injection of allobarbitone (Dial, Ciba), 130 mg kg^{-1}, for pulmonary resistance and compliance measurement which required simultaneous and continuous recording of transpulmonary pressure, air flow and volume change. Transpulmonary pressure was determined by means of a differential pressure transducer connected to both an intrapleural and a tracheal cannula. Tracheal air flow was determined with the aid of a Fleisch tube and integration of this signal provided information on volume change (Daly, Farmer & Levy, 1971). Spontaneously respiring guinea-pigs were used since it was found that artificial ventilation obscured the bronchodilator response. Recordings were made until pulmonary resistance and compliance were constant. An infusion of test compound was then begun into the jugular vein and continued for 5 min. Two higher concentrations of drug were infused at 30 min intervals. Effects on pulmonary resistance and compliance were calculated as change from the starting level and as % of the maximum response obtainable to isoprenaline. The maximum response to isoprenaline, determined in a separate group of 10 animals, occurred with a total infused dose of 15 $\mu g\ kg^{-1}$. ED50 values were calculated (Table 1).

Relatively small but statistically significant changes (up to 30%) in pulmonary resistance and compliance were obtained. All the drugs tested were capable of achieving the same maximum response as isoprenaline while the doses used and relative activities are comparable with those of Carney, Daly & others (1971) for the guinea-pig tracheal chain and Konzett-Rössler preparations.

Because we have shown that some drugs cause similar changes in pulmonary compliance and resistance, techniques such as the Konzett-Rössler preparation (which depend on changes in compliance) may be thought of as satisfactory in the evaluation of bronchodilator drugs. However, there could be advantages when investigating novel drugs in using a method which distinguishes possible sites of

Table 1. *Effects of intravenously administered isoprenaline, isoetharine, papaverine and aminophylline on pulmonary resistance and compliance in the anaesthetized spontaneously respiring guinea-pig.*

Drug	Total dose infused kg^{-1}	*Pulmonary resistance decrease* mean % ± s.e.	% of maximum response to isoprenaline	ED50 kg^{-1}	*Pulmonary compliance increase* mean % ± s.e.	% of maximum response to isoprenaline	ED50 kg^{-1}
Saline	0·5 ml	0·9 ± 0·9	—	—	3·1 ± 2·6	—	—
	0·5 ml	3·9 ± 2·3	—		1·4 ± 0·9	—	
	0·5 ml	2·6 ± 2·6	—		4·2 ± 2·3	—	
Isoprenaline	0·2 μg	8·5 ± 2·6	29·8	1·5 μg	5·9 ± 2·0	20·7	1·5 μg
	1·0 μg	12·9 ± 2·0*	45·3		13·3 ± 5·3	46·7	
	5·0 μg	17·8 ± 1·9**	62·5		25·7 ± 3·1**	90·2	
Isoetharine	1·0 μg	9·0 ± 2·3	31·6	8·6 μg	9·7 ± 4·0	34·0	3·6 μg
	5·0 μg	14·2 ± 3·9*	49·8		14·0 ± 7·7*	49·1	
	20·0 μg	15·2 ± 4·8*	53·3		22·7 ± 8·3*	79·6	
Papaverine	0·5 mg	4·8 ± 1·6	16·8	2·2 mg	2·9 ± 2·3	10·2	2·7 mg
	2·0 mg	15·3 ± 0·7**	53·7		12·9 ± 4·0	45·3	
	8·0 mg	21·0 ± 3·0**	73·7		21·2 ± 2·8**	74·4	
Aminophylline	0·5 mg	8·8 ± 2·9	30·9	5·0mg	7·7 ± 2·8	27·0	2·6mg
	2·5 mg	8·8 ± 5·0	30·9		10·5 ± 2·6	36·8	
	12·5 mg	17·6 ± 3·4*	61·8		23·6 ± 3·1*	82·8	

From *t*-test comparing control and test value
*$P = <0·05$ **$P = <0·001$
s.e. = standard error of the mean for each group of 5

action in the respiratory tree, especially since Colebatch (1970) reported that bronchoconstrictor agents preferentially altered pulmonary resistance, indicating greater activity on conducting than on peripheral airways.

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