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PULMONARY MECHANICAL EFFECTS OF EXPERIMENTAL LUNG EMBOLISM AND THEIR MODIFICATION BY BRONCHODILATOR DRUGS IN THE GUINEA-PIG

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In the anaesthetized guinea-pig micro-embolism induced by barium sulphate causes marked increases in pulmonary resistance and decreases in pulmonary compliance. Bronchodilator drugs prevent these changes with salbutamol showing much greater activity on pulmonary resistance changes than compliance changes. The results are discussed with regard to the site of action in the respiratory tree and potential clinical use.

Pulmonary microembolism has been studied for its effects on respiration in a large number of species (see Whitteridge, 1950). Halmagyi & Colebatch (1961) have shown that barium sulphate embolism in sheep produces a sharp fall in compliance, and by inference a rise in pulmonary resistance, which can be antagonized by isoprenaline. Similarly, Cahill, Attinger & Byrne (1961) have shown bronchoconstriction following embolism in the dog. However, the published work on microembolism does not appear to include a study of barium sulphate embolism and its antagonism by drugs in the guinea-pig, which is a widely used species for respiratory studies. Accordingly, an investigation has been carried out to study barium sulphate microembolism in the guinea-pig and to investigate modification of the resultant pulmonary mechanical changes by a variety of bronchodilator drugs.

Methods Male albino guinea-pigs weighing 350-500 g and kept overnight without food, were anaesthetized by intraperitoneal injection of allobarbitone (Dial) 137 mg/kg and prepared for the measurement of pulmonary resistance and compliance as described by Daly, Farmer & Levy (1971). In addition the external jugular vein was cannulated and a catheter inserted until its tip was positioned in the right auricle. After completion of the setting up procedure the lungs were forcibly inflated to reverse any positional atelectasis. Recordings of pulmonary resistance and compliance were taken at 0, 10, 20 and 30 minutes. At 30 min a slow infusion of saline (0.9% w/v NaCl solution) or test solution into the right auricle was begun with a Palmer continuous slow injector. The infusion was continued for 5 min until a volume of 1.4 ml had been injected. Recordings were taken 1, 2, 3, 4 and 5 min after starting the infusion. Immediately after the infusion, an injection of barium sulphate (0.5 ml/kg) (30% w/v suspension) was given into the right auricle. Continuous recordings were taken from the moment of injection until maximum response was obtained which was almost invariably within 1 minute. The lungs were then forcibly inflated and recordings taken 10, 20 and 30 min after inflation. Saline was then infused for 5 min and the dose of barium sulphate repeated. Each drug dose level was administered to a group of 5 animals and the mean response compared with that of the control group. ED_{50} values were determined from regression lines calculated by the method of least squares.

Results Fifteen animals received saline alone before challenge with barium sulphate which caused a rise in pulmonary resistance of 194.4% ± 28.2 (mean ± s.e.) and a decrease in pulmonary compliance of 75.0% ± 4.4. The effects of test drugs on barium sulphate induced pulmonary mechanical changes are summarized in Table 1.

Discussion Microembolism following intravenous injection of a barium sulphate suspension into the anaesthetized guinea-pig resulted in an elevation of pulmonary resistance and decrease of pulmonary compliance. The dose of embolic material used was similar to that used in sheep and cats (Halmagyi & Colebatch, 1961; Nadel, Colebatch & Olsen, 1964). Histological studies by Nadel *et al.* (1964) on cat lungs rapidly frozen after pulmonary embolism showed that barium sulphate had lodged in the pulmonary arterioles and peripheral lung units were constricted. The alveolar ducts were constricted markedly but distal bronchioles were less affected.

The effects of isoprenaline and salbutamol in

Table 1 Effects of bronchodilators in antagonizing the enhanced pulmonary resistance and decreased pulmonary compliance induced by barium sulphate microembolism in the anaesthetized guinea-pig

Drug	*Dose* ($\mu g\ kg^{-1}\ min^{-1}$)	*% Inhibition of pulmonary resistance response (mean ± s.e.)*	ED_{50}* ($\mu g\ kg^{-1}\ min^{-1}$ *resistance)*	*% Inhibition of pulmonary compliance response (mean ± s.e.)*	ED_{50}* ($\mu g\ kg^{-1}\ min^{-1}$ *compliance)*	$\frac{ED_{50}\ compliance}{ED_{50}\ resistance}$
Isoprenaline	0.030	39.2 ± 6.6	0.12 (0.005-0.5)	19.4 ± 4.2	0.22 (0.06-0.8)	1.8
	0.125	52.4 ± 16.1		40.8 ± 17.5		
	0.250	66.0 ± 13.0		52.6 ± 5.1		
	1.000	78.9 ± 10.0		76.7 ± 8.2		
	4.000	94.1 ± 1.9		91.1 ± 2.7		
Isoetharine	0.250	32.3 ± 12.8	0.34 (0.03-4.9)	13.6 ± 4.3	2.92 (0.4-58)	8.6
	1.000	63.9 ± 9.2		31.5 ± 13.4		
	4.000	86.2 ± 4.3		60.9 ± 8.1		
Salbutamol	0.063	39.7 ± 14.7	0.11 (0.003-0.4)	8.8 ± 7.8	11.1 (2.88-185)	100.9
	0.250	58.6 ± 12.5		22.8 ± 8.4		
	1.000	81.0 ± 5.4		33.7 ± 11.5		
	4.0	95.4 ± 2.4		44.4 ± 7.9		
	16.0	100.0 ± 0.0		54.4 ± 7.4		
Papaverine	50.0	25.2 ± 16.3	80 (11-392)	11.9 ± 8.6	240 (70-1100)	3.0
	100.0	59.2 ± 15.4		37.4 ± 12.0		
	500.0	91.0 ± 5.1		59.0 ± 14.3		
	2000.0	97.3 ± 1.4		90.1 ± 6.4		
Aminophylline	500.0	39.5 ± 18.3	670 (60-9500)	19.5 ± 10.8	1180 (224-8326)	1.8
	1000.0	56.7 ± 15.0		41.9 ± 13.9		
	2500.0	89.9 ± 5.2		74.1 ± 9.7		

* Figures in parentheses are 95% confidence limits.

inhibiting embolism induced compliance changes were very similar to those observed by Carney, Daly, Lightowler & Pickering (1971) who used the method of Konzett & Rössler (1940) which reflects pulmonary compliance rather than resistance changes. However, the bronchodilator drugs tested consistently tended to inhibit pulmonary resistance changes more readily than pulmonary compliance changes. This selectivity was most marked for salbutamol and could be due to a preferential action on the bronchioles, higher doses being required to prevent constriction of the alveolar ducts and consequent alveolar collapse. Halmagyi & Colebatch (1961) attributed the effectiveness of isoprenaline to prevention of the actions of released constrictor agents and this is supported by Nadel *et al.* (1964) and Mills, Sellick & Widdicombe (1969). The latter workers extended this theory by proposing that an action on the smooth muscle, local to the lung irritant receptors, could prevent their activation and so forestall reflex bronchoconstriction. Thus while isoprenaline is generally agreed to be effective in antagonizing bronchospasm induced by pulmonary embolism, the mechanism has not been fully elucidated.

Pulmonary embolism has been treated by the use of anticoagulants, together with spasmolytic drugs such as papaverine (Boyer & Curry, 1944) and isoprenaline (Dalen & Dexter, 1969). In the present study the most potent compounds found to inhibit the pulmonary mechanical changes to barium sulphate in the anaesthetized guinea-pig were the β-adrenoceptor stimulant drugs. Isoprenaline was not much more active than the selective β_2-adrenoceptor stimulant salbutamol indicating that an action on β_1-adrenoceptors to cause a positive inotropic effect is unnecessary. Papaverine and aminophylline both inhibit the enzyme phosphodiesterase and the former has strong inotropic properties but was only weakly active in this test. It is difficult to speculate on the importance of pulmonary vasodilation since the β-adrenoceptor stimulants and the spasmolytics, papaverine and aminophylline all have this action. The evidence indicates that bronchodilator and not positive inotropic activity is the important feature of those drugs useful in preventing the effects of pulmonary microembolism in the anaesthetized guinea-pig. In the light of these results, salbutamol may be worthy of clinical investigation in cases of pulmonary embolism.

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