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Inhibition of bronchoconstriction by aerosol of a lipid emulsion containing prostaglandin E_1

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Some prostaglandins, like PGE_1 and PGE_2, have proved to be effective bronchodilators in animals (Rosenthale et al 1971; Wassermann et al 1980), but PGE_1 has not been needed as a bronchodilator because of its irritant property (Smith et al 1975). To decrease the irritant property, we have incorporated it in a lipid emulsion (Intralipid, average of particle diameter 0·2 μm) widely used for parenteral nutrition in man, and used thus as an aerosol for the treatment of bronchoconstriction.

PEG_1 and PGE_1-CD (PGE_1 cyclodextrin, Prostandin) were kindly supplied by Ono Pharm. Co., Ltd, Osaka, Japan. PGE_1 was dissolved in soybean oil at 300 μg ml^{-1}, and incorporated in a lipid emulsion (lipo-PGE_1) prepared in a manner similar to that described by Mizushima et al (1982 a,b). The final concentration of PGE_1 in the lipo-PGE_1 was 30 μg ml^{-1}.

Male guinea-pigs, 230–330 g, were placed in a box (24 × 24 × 24 cm^3) equipped with a nebulizer by means of which an aerosol of a mixture of histamine hydrochloride (final conc. 0·05%) and PGE_1-CD solution, or lipo-PGE_1, was sprayed at 0·085 ml min^{-1} into the box.

All guinea-pigs not treated with PGE_1 sneezed 1–2 min after exposure and developed a mild and then severe dyspnoea within 6 min (Table 1). Aerosolized PGE_1 given as a solution and as the lipid emulsion both significantly delayed the onset of, and decreased the severity of, dyspnoea (P <0·01–0·05). The potencies of the bronchodilating property of lipo-PGE_1 and PGE_1-CD were similar (Table 1: P >0·05 at a dose of 30 μg).

Six male and 4 female volunteers inhaled aerosols of lipo-PGE_1 and PGE_1-CD in a cross over test. Lipo-PGE_1 and PGE_1-CD were given for 5 min at rates of 0·6 or 6 μg/0·2 ml min^{-1}, and 0·6 μg/0·2 ml min^{-1} respectively and the degree of irritation in the upper respiratory tracts recorded.

None of volunteers given 3 μg (0·6 μg min^{-1}) lipo-PGE_1 complained of irritation, which the rate of 6 μg min^{-1} caused a minor sore throat and cough in 2 of 10 and a moderate response in 4 of 10. PGE_1-CD at 0·6 μg min^{-1} caused a minor irritation in 2 of 10 and a moderate response in 4 of 10 (P <0·01 by χ^2 test between lipo-PGE_1 0·6 μg min^{-1} and PGE_1-CD 0·6 μg min^{-1}). Therefore, the irritant effect of lipo-PGE_1 aerosol on the upper respiratory tract in man seemed to be some 10 times weaker than that of PGE_1-CD.

A beneficial effect of PGE_1 aerosol was observed in some patients with bronchial asthma, but an irritation in the upper respiratory tract and an aggravation of respiratory function were observed by Smith et al (1975). We have found lipo-PGE_1 to have a similar bronchodilating action to, and much less irritation than, PGE_1-CD, suggesting the possibility of its clinical use in the treatment of bronchoconstriction in man.

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Table 1. Effects of aerosolized PGE_1 (PGE_1-CD) and lipo-PGE_1 (PGE_1 in lipid emulsion) on histamine-induced dyspnoea in conscious guinea-pigs.

		Onset of dyspnoea			Onset of severe dyspnoea		
		2 min	5 min	10 min	5 min	10 min	Death
	Control	6/6[a]	6/6	6/6	6/6	6/6	2/6
PGE_1	5 μg ml^{-1}	1/6*	4/6	6/6	2/6	4/6	2/6
	10 μg ml^{-1}	0/6**	4/6	6/6	3/6	5/6	2/6
	30 μg ml^{-1}	0/6**	1/6*	2/6	1/6*	2/6	2/6
Lipo-PGE_1	30 μg ml^{-1}	0/6**	0/6**	3/6	0/6**	1/6*	0/6

(a) Represents the appearance of dyspnoea or severe dyspnoea evoked by histamine within each indicated time (min); Number of animals with the behavioural disorder/number of animals tested. *: P <0·05, **: P <0·01 in relation to control (χ^2-test). No significant difference (P >0·05) between PGE_1 30 μg ml^{-1} and lipo-PGE_1 30 μg ml^{-1}.

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