Br. J. Pharmac. (1977), **60**, 607–608

THE EFFECT OF ZINC ON ANAPHYLAXIS *in vivo* IN THE GUINEA-PIG

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The protective effects of pretreatment with zinc sulphate aerosols against bronchoconstriction induced by egg albumen or histamine aerosols were assessed in sensitized or non-sensitized guinea-pigs respectively. Pretreatment with an adequate concentration of zinc sulphate aerosol significantly prolonged the time of onset of bronchoconstriction in sensitized guinea-pigs challenged with egg albumen, but did not appreciably alter the onset time of histamine-induced bronchoconstriction in non-sensitized animals. These findings suggest that zinc aerosols may be of prophylactic value against bronchoconstriction of allergic origin.

Introduction It is generally believed that anaphylactic reactions are produced by the release of autacoids from target cells, especially mast cells, as a consequence of antigen-antibody interaction (Austen, 1974). Inhibition of histamine and slow reacting substance of anaphylaxis (SRS-A) release from the mast cells, e.g. by disodium cromoglycate, has been shown to be effective in the prophylactic treatment of bronchial asthma (Dykes, 1974; Garland & Mongar, 1974).

In vitro experimental evidence indicates that zinc ions selectively stabilize the membrane of mast cells from the peritoneum or lungs of rats, and significantly inhibit disruption of these cells by compound 48/80, lecithinase A or antigen-antibody interactions to prevent histamine release (Högberg & Uvnäs, 1960; Kazimierczak & Maśliński, 1974). Thus, it is possible that zinc ions might have a cromoglycate-like action against bronchoconstriction following anaphylaxis.

The purpose of this investigation was to study the effects of pretreatment with zinc sulphate aerosols on bronchoconstriction induced by anaphylaxis *in vivo* in guinea-pigs.

Methods Guinea-pigs of either sex, weighing 400–550 g, were used. One group was sensitized to egg albumen by an intramuscular injection of 0.7 ml of a 5% solution of crystalline egg albumen (BDH), prepared in 0.9% w/v NaCl (saline), 3 weeks before challenge (Herxheimer, 1952). At the start of the experiment, each animal was put into a plastic observation chamber (350 x 190 x 280 mm) and anaphylaxis was induced by an aerosol of the same solution of antigen introduced into the closed chamber. The onset of marked dyspnoea was taken as the end-point, and the duration of exposure required to produce bronchoconstriction was recorded. In the group of non-sensitized guinea-pigs, bronchoconstriction was induced by an aerosol of freshly prepared 2% w/v histamine diphosphate (expressed as the salt; Sigma) in saline (final pH 4.1). A finely atomized mist of either egg albumen or histamine solution was produced by a nebulizer connected to a compressor pump (pressure 120 mmHg). The solutions were atomized at a rate of 0.025 ml/minute.

The protective effect of zinc sulphate ($ZnSO_4.7H_2O$; May & Baker) against bronchoconstriction induced by aerosols of egg albumen in sensitized guinea-pigs or of histamine in non-sensitized animals was assessed by exposing the animals to an aerosol of this agent for 5 min immediately before starting the experiments. Zinc sulphate was dissolved in saline (20, 40 or 80 mg/ml w/v; expressed as the salt including its water of crystallization) before use (final pH 4.8). Th pH of saline aerosols given to the controls was adjusted to 4.8 to obviate possible bronchial tissue pH changes which might interfere with the release, diffusion or activity of histamine following anaphylaxis, or its diffusion and activity following inhalation.

Results In sensitized guinea-pigs, challenge with an aerosol of 5% egg albumen produced anaphylaxis characterized by marked dyspnoea. Pretreatment with zinc aerosols prolonged the time of onset of dyspnoea, and statistical significance was reached with concentrations of 40 and 80 mg/ml ($P < 0.01$ for both, Table 1).

In non-sensitized guinea-pigs, exposure to an aerosol of 2% histamine also induced bronchoconstriction characterized by marked dyspnoea. However, pretreatment with zinc aerosols, at concentrations which significantly protected sensitized animals from anaphylaxis, did not appreciably alter the time of onset of dyspnoea.

Discussion The ability of pretreatment with zinc aerosols to delay significantly the onset of bronchoconstriction induced by antigen challenge in sensitized guinea-pigs is probably due to membrane stabilization

Table 1 The effects of pretreatment with zinc aerosols against bronchoconstriction induced by aerosols of egg albumen in sensitized guinea-pigs or of histamine in non-sensitized guinea-pigs

	Exposure time required to produce bronchoconstriction (min)	
Pretreatment	*Egg albumen (5%)*	*Histamine diphosphate (2%)*
Saline	2.81 ± 0.23 (8)	1.39 ± 0.09 (12)
Zinc sulphate		
20 mg/ml	3.26 ± 0.14 (8)	–
40 mg/ml	4.83 ± 0.53 (8)*	1.45 ± 0.12 (11)
80 mg/ml	4.25 ± 0.37 (8)*	1.52 ± 0.09 (12)

Each value is the mean ± s.e. mean of the number of animals given in parentheses. *$P < 0.01$ when compared with the saline-pretreated control using Student's t test.

of the mast cells, and consequent inhibition of the release of autacoids by the antigen-antibody interaction (Mota & Vugman 1956; Högberg & Uvnäs, 1960). This effect appears to be similar to that produced by cromoglycate when used for bronchial asthma in man. However, pretreatment with cromoglycate aerosols, with concentrations as high as 100 mg/ml, did not significantly delay the onset of antigen-induced bronchoconstriction (unpublished observations); this is in accord with the observation of Assem & Mongar (1970) that cromoglycate is unable to prevent anaphylactic release of histamine from guinea-pig lungs. Our findings are not at variance with the idea that zinc may have acted through a different mechanism to stabilize the mast cell membrane.

The possibility of zinc acting as a physiological antagonist, or as a local irritant by stimulating mucus secretion in the bronchial tree to prevent contact of the antigen with the bronchial mucosa, cannot be excluded. These effects are unlikely because pretreatment with zinc aerosols did not protect the non-sensitized guinea-pigs from bronchoconstriction induced by histamine aerosols.

Our results suggest that zinc aerosols may be useful for preventing bronchoconstriction in anaphylactic reactions and in bronchial asthma. However, since cromoglycate is ineffective in guinea-pigs, the possibility of species difference in the activity of zinc has also to be borne in mind.

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(Received April 5, 1977.)