

The effect of inhaled verapamil on allergen-induced bronchoconstriction

K. R. PATEL, M. R. AL SHAMA and J. W. KERR

Department of Respiratory Medicine, Western Infirmary, Glasgow

(Received 12 February 1982; accepted for publication 4 March 1982)

Summary

In eight patients with extrinsic bronchial asthma the effect of inhaled verapamil (3 and 6 mg) was compared with saline on bronchial challenge with extracts of *Dermatophagoides pteronyssinus*. There was no significant difference in the baseline FEV₁ before and after inhalation of saline or verapamil 2.5 mg/ml. However, verapamil at a higher concentration (5 mg/ml) caused bronchoconstriction in four patients who had to be excluded from the part of the study. Verapamil at both these concentrations failed to have an effect on the allergen-induced bronchoconstriction. These findings suggest that verapamil given by inhalation does not prevent mediator release from the lung mast cells following specific allergen challenge.

Introduction

The release of chemical mediators from the lung mast cell and bronchial reactivity to these mediators are two important components in allergic asthma. The activation and the liberation of mediators from the mast cell and the contraction of bronchial smooth muscle are both dependent on the influx of free calcium ions across the cell membrane (Austen & Orange, 1975; Coburn, 1977). Calcium antagonists, verapamil and nifedipine, are effective in preventing transmembrane influx of calcium ions and recently both these drugs have been shown to prevent exercise-induced asthma (Patel, 1981a, Cerrina *et al.*, 1981a). *In vitro*, verapamil and nifedipine have been shown to inhibit anaphylaxis in the airway smooth muscle (Weiss & Marowicz, 1981) and also to prevent the release of platelet-activating factor (PAF) and slow-reacting substance of anaphylaxis (SRS-A) from the human neutrophils (Cerrina *et al.*, 1981b). We have therefore investigated the effect of inhaled verapamil on allergen-induced bronchoconstriction in patients with asthma.

Patient and methods

Eight patients aged 18–33 years with extrinsic bronchial asthma and reversible airflow

Correspondence: Dr K. R. Patel, Department of Respiratory Medicine, Western Infirmary, Glasgow G11 6NT.

obstruction were studied. All patients had positive prick tests to *Dermatophagoides pteronyssinus* and other common inhalant allergens. Bronchodilator aerosol and sodium cromoglycate were stopped for at least 12 hr. Patients on oral or inhaled corticosteroids, antihistamine and anticholinergic agents were excluded from the study. The nature and purpose of the investigations were explained to each subject and informed consent obtained. The study was approved by the Hospital Ethical Committee.

Forced expiratory volume in one second (FEV₁) was measured on a water sealed spirometer (Godart Pulmotest). Initially the manoeuvre was repeated until three reproducible tracings were obtained and the best of these was recorded. After the bronchial challenge with *D. pteronyssinus* extract, however, the FEV₁ was measured once only, unless the measurement was technically unsatisfactory. Volumes were corrected to BTPS. All solutions were inhaled through a Wright nebulizer at tidal breathing using compressed air at a flow rate of 9 l/min (18 psi). The inhalations were carried out randomly on a single blind basis.

Experimental procedure

After the baseline recording of FEV₁, saline (9 g/l) or verapamil (2.5 or 5 g/l) was inhaled through a Wright nebulizer for 5 min. The dose of verapamil nebulizer was 3 and 6 mg. The FEV₁ was recorded 30 min later. This was followed by 2-min inhalations of extract of *D. pteronyssinus* (Bencard) through a Wright nebulizer in two-fold increasing concentration from 60 to 960 µg/ml. (dry weight/volume) at 15-min intervals. After each allergen inhalation FEV₁ was recorded at 0.5, 1, 3, 5, 7 and 10 min and subsequent intervals of 5 min to obtain the lowest post-inhalation FEV₁. The FEV₁ was recorded only once on these occasions unless the measurement was technically unsatisfactory. Inhalations were continued until the FEV₁ had fallen by 20% or more. The change in FEV₁ was calculated from the post-saline or post-verapamil baseline. The responses were expressed in terms of provoking concentrations of allergen producing a 20% fall in FEV₁ (PC₂₀) and calculated by the formula:

$$\frac{\text{Concentration of allergen inhaled } (\mu\text{g/ml}) \times 20}{\% \text{ Fall in FEV}_1}$$

Results

The results are given in Table 1. In eight patients there was no significant difference in the pretreatment or post-treatment values of FEV₁ after saline or verapamil (2.5 mg/ml) inhalations. However, in 4 patients (Nos. 2, 4, 6 & 8) verapamil at a higher concentration (5 mg/ml) induced significant bronchoconstriction and these patients had to be excluded from the second part of the study. Verapamil at both these concentrations failed to modify the allergen induced fall in FEV₁ and PC₂₀ for *D. pteronyssinus* in the patients studied.

Discussion

Verapamil at a concentration of 2.5 mg/ml did not affect the mean FEV₁ in the 8 patients studied. However, verapamil at a higher concentration produced a significant bronchoconstriction in 4 patients. Furthermore, verapamil at both the concentrations used in the study failed to inhibit allergen induced bronchoconstriction.

The activation of mast cell and the liberation of chemical mediators are both

Table 1. The effect of Verapamil on PC₂₀ for *D. pteronyssinus* induced bronchoconstriction in 8 patients.

No.	Sex	Age	Saline			2.5 mg/ml			Verapamil 5 mg/ml		
			Baseline Before	Baseline After	PC ₂₀ µg/ml	Baseline Before	Baseline After	PC ₂₀ µg/ml	Baseline Before	Baseline After	PC ₂₀ µg/ml
1	M	27	5.86	5.69	1864.0	5.33	5.02	1989.0	5.35	5.26	1505.5
2	M	23	3.51	3.40	39.9	3.82	3.82	32.2			
3	M	23	4.42	4.38	112.4	4.12	4.18	76.7	4.02	3.67	74.8
4	M	18	3.11	3.11	74.8	3.10	2.95	77.2			
5	M	32	2.91	3.05	82.2	2.91	3.16	77.4	3.05	2.93	82.2
6	M	33	3.05	2.68	30.1	2.61	2.38	25.3			
7	F	18	3.68	3.58	208.2	3.68	3.68	179.4	3.35	3.25	385.5
8	M	18	3.65	3.70	23.2	3.45	3.38	21.2			
Mean		24	3.77	3.70	304.4	3.63	3.57	309.8	3.94	3.78	498.4
SEM			0.34	0.34	223.8	0.30	0.29	240.0	0.51	0.52	218.0
p (Saline v/s Verapamil)					NS			NS			NS

NS: Not significant.

SEM: One standard error of mean.

dependent on calcium ions (Austen & Orange, 1975). Calcium ion movement from the extracellular to the intracellular compartment of the mast cell can initiate histamine release even in the absence of antigen (Foreman, Mongar & Gomperts, 1973). In contrast, the exclusion of calcium ions can inhibit mediator release from the mast cell *in vitro*. Nifedipine and verapamil both inhibit transmembrane influx of calcium ions, and in various smooth muscle preparations produce relaxation and suppression of calcium-dependent membrane excitation (Fleckenstein, 1977). In addition, calcium antagonists by blocking excitation contraction coupling are also capable of neutralising the vaso-constrictor effect of histamine, serotonin and acetylcholine (Fleckenstein-Grün, Fleckenstein, Byon & Kim, 1978). The failure of inhaled verapamil to modify allergen-induced bronchoconstriction in the patients studied suggests that calcium antagonists given by inhalation do not prevent mediator release from the lung mast cell following specific antigen challenge. These observations are consistent with a recent report of Butchers, Skidmore, Vardey & Wheeldon, (1981) who failed to demonstrate an antigen-induced release of spasmogens from sensitised fragments of the human lung by calcium antagonists. In addition, verapamil and nifedipine do not modify histamine bronchial reactivity in asthmatic patients (Patel, 1981b; personal observations). The beneficial effect of calcium antagonists in exercise-induced asthma is likely to be on the non-specific degranulation of the lung mast cell which is probably calcium dependent but different from the allergen induced mediator release.

Acknowledgements

I would like to thank Mrs Rita Jack for technical assistance. The study was supported by a grant from Abbott Laboratories Ltd.

References

- AUSTEN, K.F. & ORANGE, R.P. (1975) Bronchial asthma: the possible role of chemical mediators of immediate hypersensitivity in the pathogenesis of subacute chronic disease. *American Review of Respiratory Disease*, **112**, 423.
- BUTCHERS, P.R., SKIDMORE, I.F., VARDEY, C.J., & WHEELDON, A. (1981) Calcium antagonists in exercise-induced asthma. *British Medical Journal*, **282**, 1972.
- CERRINA, J., DENJEAN, A., ALEXANDRE, G., LOCKHART, A. & DUROUX, P. (1981a) Inhibition of exercise-induced asthma by a calcium antagonist, nifedipine. *American Review of Respiratory Disease*, **123**, 156.
- CERRINA, J., JOUVIN, E., DUROUX, P. & BENVENISTE, J. (1981a) Inhibition of the release of platelet-activating factor and slow-reactive substance from human neutrophils by the calcium antagonist nifedipine. *American Review of Respiratory Disease*, **123**, Supplement 4:44.
- COBURN, R.F. (1977) The airway smooth muscle cell. *Federation Proceedings*, **36**, 2692.
- FLECKENSTEIN, A. (1977) Specific pharmacology of calcium in myocardium pacemakers, and vascular smooth muscle. *Annual Review of Pharmacology & Toxicology*, **17**, 149.
- FLECKENSTEIN-GRÜN, G., FLECKENSTEIN, A., BYON, Y.K. & KIM, K.W. (1978) Mechanism of action of Ca^{++} antagonists in the treatment of coronary disease with special reference to perhexiline maleate. Proceedings of Symposium of Perhexiline Maleate, 1-22. *Excerpta Medica, Amsterdam*.
- FOREMAN, J.C., MONGAR, J.L. & GOMPERTS, B.D. (1973) Calcium ionophores and movement of calcium ions following the physiological stimulus to a secretory process. *Nature, London*, **245**, 249.
- PATEL, K.R. (1981a) Calcium antagonists in exercise induced asthma. *British Medical Journal*, **282**, 932.
- PATEL, K.R. (1981b) The effect of verapamil on histamine and methacholine-induced bronchoconstriction. *Clinical Allergy*, **11**, 441.
- WEISS, E.B. & MARKOWICZ, J. (1981) Inhibition of anaphylaxis in airway smooth muscle by the calcium channel drugs, verapamil and nifedipine. *American Review of Respiratory Disease*, **123**, Supplement 4:42.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.