Inhalation of Calcium Channel Blocking Agents Protects Against Methacholine-Induced Bronchoconstriction

Takako TSUDA, Makoto HATTA, Kiyoshi ISHIKAWA, Takashi NAKAGAWA, Norihumi MABUCHI, Hiroshi ANDO and Osamu NISHIDA

The calcium channel blockers, diltiazem and verapamil, and the beta agonist orciprenaline sulfate all demonstrated significant protection against methacholine-induced bronchoconstriction in 11 stable asthmatics (5 males and 6 females). Ten and 20 mg of inhaled diltiazem, 5 mg of verapamil or 30 mg of orciprenaline administered 15 min before stepwise increasing doses of methacholine hydrochloride produced significant reduction in respiratory resistance (Rrs), minimum dose of methacholine hydrochloride required for Rrs increase (Dmin) and bronchial reactivity measured with an Astograph. The mechanism of action of the calcium channel blockers is presumably at the level of the smooth muscle cells themselves. The combination of positive influence and lack of any adverse effect on blood pressure or heart rate with any of the agents tested indicates that their clinical application for alleviation of acute asthma can be recommended. (Key words: stable asthmatics, calcium channel blockers, methacholine hydrochloride, Astograph, respiratory resistance)

(Tsuda T, Hatta M, Ishikawa K, et al.: Inhalation of calcium channel blocking agents protects against methacholine-induced bronchoconstriction. J Anesth 7: 397–404, 1993)

Calcium-dependent excitation-contraction and stimulus-secretion coupling mechanisms play central roles in the pathophysiology of airway obstruction. Interest has therefore been concentrated on the possibility that Ca^{++} antagonists might be useful as an adjunct in the treatment of acute phase asthma[1]. While some clinical evidence has been generated indicating that this might be the case [2–4], a number of studies have revealed no significant beneficial influence[5–8]. Whether this is dependent on the actual agent used or the route of application remains unclear although it has been suggested that the most commonly adopted oral mode of administration is less effective. The present study was designed to examine and compare the bronchodilating effects of two organic calcium channel blocking agents (diltiazem and verapamil) on bronchocon-

Department of Anesthesiology and Resuscitology, Nagoya City University Medical School, Nagoya, Japan

Address reprint requests to Dr. Tsuda: Department of Anesthesiology and Resuscitology, Nagoya City University Medical School, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya, 467 Japan

Table. Eleven stable asthmatics, five men and six women, 17 to 57 years old, gave informed consent for the study. Four demonstrated the atopic, five the infective and two the mixed type of the disease

Subject No.	Age (Yr)	Sex	Type of Asthma	Duration of Asthma (Yr)
1	17	M	Atopic	16
2	35	M	Atopic	6
3	37	F	Atopic	13
4	35	F	Atopic	12
5	34	F	Infective	9
6	52	M	Infective	17
7	56	M	Infective	19
8	57	M	Infective	2
9	52	F	Infective	12
10	47	F	Mixed	14
11	55	F	Mixed	24

striction known to be induced by the direct acting chemical methacholine hydrochloride[9]. Since beta agonists, including orciprenaline sulfate (metaproterenol), have found general use for management of asthma patients[10–12] this β_2 specific adrenergic agent was also included for comparison of influence exerted when applied by the inhalation route.

Materials and Methods

Subjects

Eleven stable asthmatics (5 men and 6 women) between 17 and 57 years of age presenting as out-patients at Nagoya City University Hospital were studied (table). All subjects met the criteria used for definition of stable asthma published by the American Thoracic Society[13]. The patients had all undergone previous methacholine challenge assessment, with acceptable results. All subjects were non-smokers. Bronchodilator medication was withheld in all cases at least 12 hours prior to commencement of the measurements. Similarly no steroid preparations were administered within the previous 24 hour period. None of the patients had respiratory tract infection or acute attacks within two weeks before the treatment testing. Informed consent was obtained from all patients and the study adhered to the guidelines of Nagoya City University for human experimentation.

Equipment and Materials

The calcium channel blockers diltiazem (Tanabe Pharmaceutical Co., Ltd., Osaka, Japan) and verapamil (Eizai Pharmaceutical Co., Ltd., Tokyo, Japan) as well as the beta agonist orciprenaline sulfate (metaproterenol sulfate, Japan Boehringer Ingelheim Co. Ltd., Kawanishi, Japan) were all administered diluted with saline (pH 7.3) for inhalation exposure, aerosols being generated with a Bird jet nebulizer with IPPB (Bird Corporation, U.S.A.). It has previously been demonstrated that use of a jet nebulizer with IPPB is superior to the metered dose inhaler (MDI) for delivery of bronchodilator aerosols. The 'Astograph' direct-recording equipment used (TCK-6100H, Chest Co., Tokyo, Japan)[14] included a bank of jet nebulizers to allow gradual increase in the dose of methacholine hydrochloride (Daiichi Pure Chemicals Co., Ltd.,

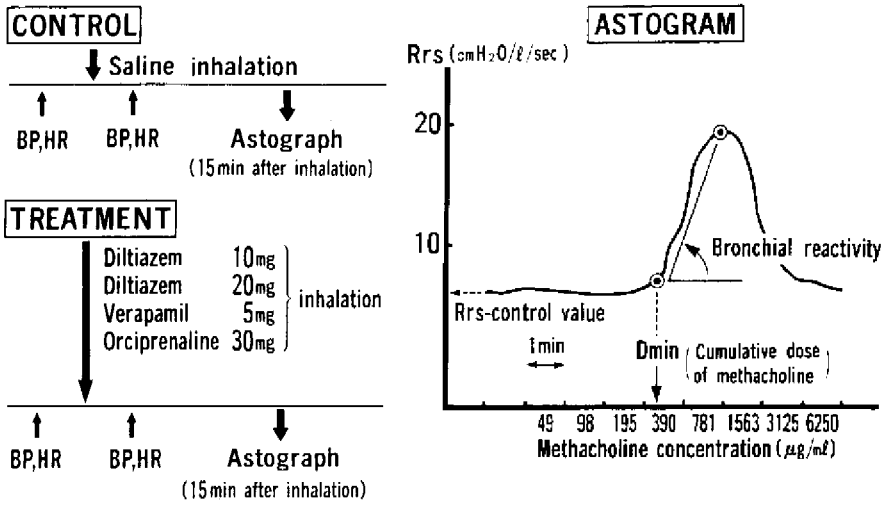

Fig. 1. An 'Astograph' (TCK-6100H, Chest Co., Ltd., Tokyo, Japan) was used to measure bronchial hyper-responsiveness 15 min after inhalation of saline (for control), diltiazem, verapamil or orciprenaline sulfate. Bronchial hyper-responsiveness was examined by direct recording of the dose-response curves of respiratory resistance (Rrs in Astogram) during continuous inhalation with tidal breathing of methacholine hydrochloride solution at stepwise increasing concentrations before and after treatment with inhaled saline (for control), 10 mg of inhaled diltiazem, 20 mg of inhaled diltiazem, 5 mg of inhaled verapamil or 30 mg of inhaled orciprenaline sulfate.

Bronchial hyper-responsiveness was evaluated relative to saline control respiratory resistance just before starting methacholine inhalation (Rrs-control value) in terms of the threshold dose of methacholine at the beginning of Rrs increase (Dmin) and the curvilinear slope of the dose-response curve (Bronchial reactivity).

Tokyo, Japan). Bronchial reactivity values were automatically calculated from the slope of the increase in respiratory resistance (Rrs). Airway resistance was measured continuously by the Astograph equipment.

Protocol

Bronchial hypersensitivity was examined by direct recording of the dose-response curve of Rrs ($cmH_2O \cdot l^{-1} \cdot sec^{-1}$) during continuous inhalation with tidal breathing of methacholine at stepwise increasing concentrations (49–25000 $\mu g \cdot ml^{-1}$). Recordings were made before (for pretreatment control values) and at 15 min after inhalation treatment with saline (for nontreatment controls), 10 mg of diltiazem, 20 mg of diltiazem, 5 mg of verapamil, or 30 mg of orciprenaline sulfate. In each case nebulization and completion of the administration was within 5 min. Bronchial responsiveness was evaluated to give control respiratory resistance values just before starting methacholine inhalation (Rrs-control) as well as the threshold dose of methacholine at the beginning of Rrs increase (Dmin) and the curvilinear slope of the dose-response curve (bronchial reactivity). Systolic and diastolic blood pressure and heart rate were also measured before and after treatment (fig. 1).

The subjects were tested in a seated position, with clipped nostrils and compression of the cheeks with balloons to minimize oral pressure, and were instructed to breathe normally.

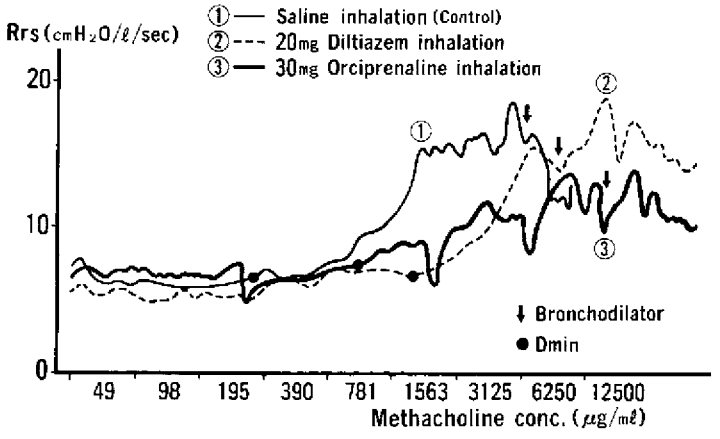

Fig. 2. Astogram trace of a 17 yr old man, suffering from atopic type bronchial asthma. The solid line (no1) denotes the Rrs after inhalation of saline as a control. The dotted line (no2) shows the results after treatment with 20 mg of diltiazem. The heavy solid line (no3) shows the results after treatment with 30 mg of orciprenaline sulfate inhalation. The large black dots representing increased Dmin show the suppression of bronchial hyperresponsiveness after treatment. The arrows show the points at which bronchodilator was administered through the Astograph apparatus.

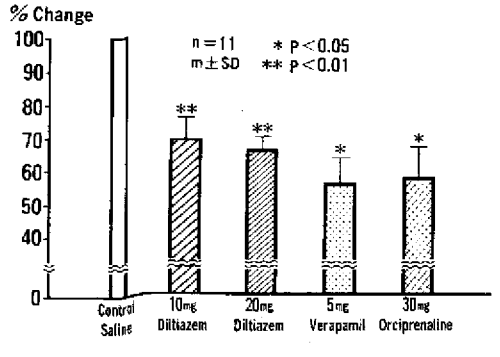

Fig. 3. Change of relative Rrs-control values after treatment by inhalation of 10 mg and 20 mg of diltiazem, 5 mg of verapamil and 30 mg of orciprenaline sulfate. As compared to the saline control level values were 68.4%, 65.6%, 55.6% and 57.1%, respectively.

Release from the bronchoconstriction induced by methacholine was achieved by appropriate administration of orciprenaline sulfate.

Statistical Analysis

Data were expressed as mean ± SD. The effects of calcium channel blockers and orciprenaline on airway responsiveness were assessed for significance using Students t test.

Results

Typical astogram traces for a young male patient after saline, diltiazem or orciprenaline administration are illustrated in figure 2.

Before methacholine challenge, Rrs values decreased to 68.4%, 65.6%, 55.6% and 57.1% of the control value after inhalation of 10 mg and 20 mg of diltiazem, 5 mg of verapamil and 30 mg of orciprenaline, respectively. The decreases in all cases were statistically significant (fig. 3). Dmin values (fig. 4) after 10 mg and 20 mg of diltiazem, 5 mg of verapamil and 30 mg of orciprenaline sulfate were 2.7 times, 4.9 times, 4.0 times, and 7.2 times larger, respectively, than the control saline

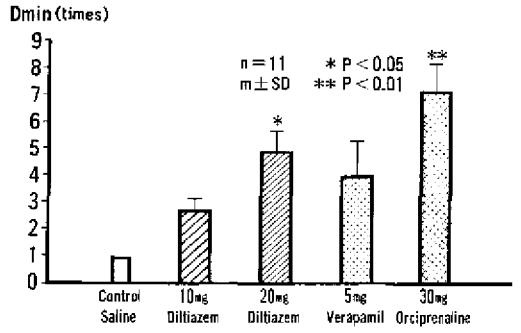

Fig. 4. Changes in Dmin values after treatment. The Dmin values were 2.7 times, 4.9 times, 4.0 times and 7.2 times larger, respectively, than the Dmin values before treatment. Significant increases of Dmin values were observed after treatment with 10 mg and 20 mg of diltiazem and orciprenaline sulfate.

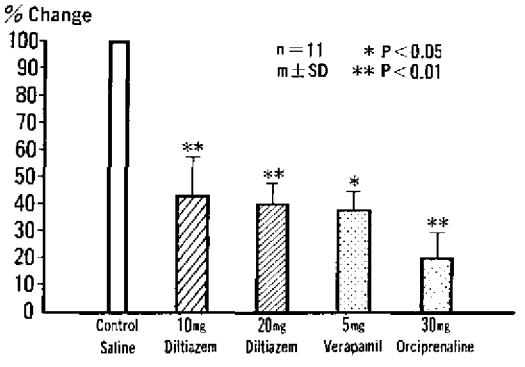

Fig. 5. Relative bronchial reactivity values after treatment. Compared to the saline control level, the values were 43.4%, 40.3%, 37.1%.

Dmin value. A significant increase was observed in the 10 and 20 mg diltiazem and 30 mg orciprenaline inhalation. Relative bronchial reactivity values decreased significantly to 43.4%, 40.3%, 37.1% and 19.8% , after 10 and 20 mg of diltiazem, 5 mg of verapamil and 30 mg of orciprenaline (fig. 5). However, no significant changes in blood pressure or heart rate were observed after inhalation of any of these drugs.

Discussion

The present data showed that inhaled diltiazem or verapamil both exerted a direct dilating effect on bronchial smooth muscles generally comparable in extent to that observed with orciprenaline. Since the beneficial effects were not accompanied by any adverse effects such as elevation of blood pressure or tachycardia, it is concluded that administration of these calcium channel blockers by the inhalation route is an effective approach for acute phase asthma patients.

While it has been generally considered that in the resting state, calcium antagonists do not have a significant influence on airway physiology[2,4,15,16] we did observe reduction in Rrs-control values with both diltiazem and verapamil. This is in line with the effects reported by Popa and her co-workers[17] where inhaled verapamil dose-dependently caused bronchodilation under both normal and histamine-pretreated conditions. Improvement of the basal bronchial tone of patients with asthma has also been described for treatment with nifedipine for four days[18]. Whether the action of calcium blockers under normal conditions involves the large or small airway remains to be elucidated.

The findings of the present study for the two calcium channel blocking agents, verapamil and diltiazem, are basically in agreement with earlier results for exercise-induced bronchoconstriction in the cases of another agent in the calcium channel blocker group, nifedipine[16] and verapamil[2], antigen-induced bronchoconstriction in the case of nifedipine[4,19] and more directly for nifedipine after methacholine[3] or histamine[15]. However they contrast with the findings of Patel[20] who described no effects of verapamil inhalation on histamine- or methacholine-induced bronchoconstriction. They are also in direct contrast to the results published by Harman and her colleagues[6] and Hartmann and

Magnussen[7] where no clinically appreciable attenuation of methacholine, histamine or exercise-induced bronchoconstriction was observed for diltiazem. There are three possible reasons for the differences in findings reported from various laboratories: 1) non-comparable parameters; 2) non-comparable doses; 3) different routes of administration.

It is likely that, at least in the diltiazem case, the earlier finding of no effect was due to the oral route chosen since the doses were very much in excess of that used in the present experiments and the protocols were also similar[6,7]. Thus it can be concluded that application of diltiazem by inhalation is more likely to be effective than with the oral route. No direct comparison with the data of Patel[20] is possible since the dose that he used was not described clearly, although the route was the same as that used in our study.

The pathogenesis of asthma potentially involves mast cells, basophils, eosinophils and other inflammatory cells, mucous glands and vagal nerve fibers as well as the smooth muscle cells[1]. Contraction of smooth muscle cells, release of chemical mediators from mast cells and basophils, nerve cell action and secretion of pro inflammatory substances are all considered to be Ca^{++}-dependent phenomena. Thus regardless of stimulus, whether it be allergen exposure, exercise, chemical reaction or cold air, an increase in free intracellular Ca^{++} is presumably involved. This has led Middleton[1] to propose a calcium hypothesis of asthma dependent on abnormal regulation through either direct or indirect effects on Ca^{++} concentration. The calcium channel blockers investigated in the present study are all considered to block potential dependent channels but the question of whether they might also exert influence on the receptor operated Ca^{++} channels activated by autocoids such as histamine or methacholine requires clarification.

In vitro studies have revealed that verapamil and nifedipine can directly inhibit smooth muscle contraction[21]. While inhibitory effects of very high doses of verapamil or nifedipine on mast cell histamine release have also been reported, these inhibitory effects cannot be expected with clinical doses[1]. In this context the findings of Henderson et al.[4] and Fish and Norman[22] are of interest since they respectively showed that nifedipine and verapamil exert their effects mainly by suppressing muscle contractility rather than by stabilizing mast cells. The conclusion of Patel based on exercise-positive[2] and methacholine-negative[20] responses, that calcium antagonists act indirectly on muscle cells via release of histamine from mast cells, is clearly not supported by their work of Henderson et al.[4] and Fish and Norman[22] and by our present findings.

Comparison of the calcium channel blockers and the beta agent on airway responsiveness revealed similar effects. Whether or not the mechanisms involved are the same in both cases is unclear. It was earlier demonstrated that verapamil administration in conjunction with isoproterenol did not reveal either additive or synergistic benefits, although it was concluded that use of these agents in combination is safe[23]. Furthermore, no negative interaction between diltiazem or nifedipine and theophylline treatment was found in chronic asthma patients[24]. Slight decrease in Pa_{O_2} values reported by Ballester et al. for nifedipine[3] and the arterial hypoxemia seen by the present authors for the β_2 agonist, procaterol[25], were not a feature of the present investigation.

In conclusion, the present results suggest that inhalation of calcium channel blockers is a safe and effective approach for management of acute

asthma where other agents are precluded. The findings documented in this paper have been presented at the 47th Annual Meeting of the Canadian Anaesthetist' Society in Vancouver, June 1990.

Acknowledgment: The authors gratefully acknowledge the constructive advice of Professor Hirotada Katsuya in preparing the manuscript.

(Received Nov. 9, 1992, accepted for publication Jan. 5, 1993)

References

1. Middleton E Jr: Calcium antagonists and asthma. J Allergy Clin Immunol 76:341–346, 1985
2. Patel KR: Calcium antagonists in exercise-induced asthma. Br Med J 282:932–933, 1981
3. Ballester E, Roca J, Rodriguez-Roisin R, et al: Effect of nifedipine on arterial hypoxaemia occurring after methacholine challenge in asthma. Thorax 41:468–472, 1986
4. Henderson AF, Heaton RW, Dunlop LS, et al: Effects of nifedipine on antigen-induced bronchoconstriction. Am Rev Respir Dis 127:549–553, 1983
5. Ritchie DM, Sierchio JN, Bishop CM, et al: Evaluation of calcium entry blockers in several models of immediate hypersensitivity. J Pharmacol Exp Therapeutics 229:690–695, 1984
6. Harman E, Hill M, Fiebelman R, et al: The effect of oral diltiazem on airway reactivity to methacholine and exercise in subjects with mild intermittent asthma. Am Rev Repir Dis 136:1179–1182, 1987
7. Hartmann V, Magnussen H: Effect of diltiazem on histamine- and carbachol-induced bronchospasm in normal and asthmatic subjects. Chest 87:174–179, 1985
8. Miadonna A, Tedeschi A, Leggieri E, et al: Effect of verapamil on allergen-induced asthma in patients with respiratory allergy. Ann Allergy 51:201–204, 1983
9. Hahn HL, Wilson AG, Graf PD, et al: Interaction between serotonin and efferent vagus nerves in dog lungs. J Appl Physiol 44:144–149, 1978
10. Salzman GA, Steele MT, Pribble JP, et al: Aerosolized metaproterenol in the treatment of asthmatics with severe airway obstruction. Comparison of two delivery methods. Chest 95:1017–1020, 1989
11. Morley TF, Marozsan E, Zappasodi SJ, et al: Comparison of beta-adrenergic agents delivered by nebulizer vs metered dose inhaler with Inspir Ease in hospitalized asthmatic patients. Chest 94:1205–1210, 1988
12. Gilman MJ, Meyer L, Carter J, et al: Comparison of aerosolized glycopyrrolate and metaproterenol in acute asthma. Chest 98:1095–1098, 1990
13. American Thoracic Society. Definitions and classifications of chronic bronchitis, asthma and pulmonary emphysema. Am Rev Respir Dis 85:762–768, 1962
14. Takishima T, Hida W, Sasaki H, et al: Direct-writing recorder of the dose-response curves of the airway to methacholine. Chest 80:600–606, 1981
15. Williams DO, Barnes PJ, Vickers HP, et al: Effect of nifedipine on bronchomotor tone and histamine reactivity in asthma. Br Med J 283:348, 1981
16. Cerrina J, Denjean A, Alexander G, et al: Inhibition of exercise-induced asthma by a calcium antagonist, nifedipine. Am Rev Respir Dis 123:156–160, 1980
17. Popa VT, Somani P, Simon V: The effect of inhaled verapamil on resting bronchial tone and airway contractions induced by histamine and acetylcholine in normal and asthmatic subjects. Am Rev Respir Dis 130:1006–1013, 1984
18. Patakas D, Vlachoianni E, Tsara V, et al: Nifedipine in bronchial asthma. J Allergy Clin Immunol 72:269–272, 1983
19. Brugman TM, Darnell ML, Hirshman CA: Nifedipine aerosol attenuates airway constriction in dogs with hyperreactive airways. Am Rev Respir Dis 127:14–17, 1983
20. Patel KR: The effect of vera-

pamil on histamine and methacholine-induced bronchoconstriction. Clin Allergy 11:441–447, 1981
21. Fanta CH, Venugopalan CS, Lacouture PG, et al: Inhibition of bronchoconstriction in the Guinea pig by a calcium channel blocker, nifedipine. Am Rev Respir Dis 125:61–66, 1982
22. Fish JE, Norman PS: Effects of the calcium channel blocker, verapamil, on asthmatic airway responses to muscarinic, histasminergic, and allergenic stimuli. Am Rev Respir Dis 133:730–734, 1986
23. Greenspon LW, Levy F: The effect of aerosolized verapamil on the response to isoproterenol in asthmatics. Am Rev Respir Dis 137:722–725, 1988
24 Christopher MA, Harman E, Hendeles L: Clinical relevance of the interaction of theophylline with diltiazem or nifedipine. Chest 95:309–313, 1989
25. Tsuda T, Yamahara T, Takasu A, et al: Clinical effects of procaterol and isoproterenol administered by nebulizer with IPPB on asthmatics (abstract in English). Kokyu (Respiration Research) 5:688–693, 1986