

Effects of Ca^{2+} Antagonist, Nicardipine, on Experimental Asthma With Special Reference to Slow Reacting Substance of Anaphylaxis

T. KOSHINO, M. FUJIMURA, S. NISHIOKA, K. OKAFUJI, S. MINAMI, K. KANAMORI, T. MATSUDA,* T. ISHIZAKI, T. SAGA and S. MIYABO**

*Third Dept. of Internal Medicine, School of Medicine, Kanazawa University, Kanazawa, and

**Third Dept. of Internal Medicine, Fukui Medical School, Fukui, Japan

Slow reacting substance of anaphylaxis (SRS-A) is an important chemical mediator of bronchial asthma. Leukotriene C_4 is a component of SRS-A and is synthesized from arachidonic acid. Its synthesizing and releasing processes are found to be Ca^{2+} -dependent. We developed an *in vivo* inhalation asthma model, mainly mediated by SRS-A, and elucidated the relationship between a Ca^{2+} -antagonist, nicardipine, and SRS-A. In the asthmatic model, mediated by endogenous SRS-A induced by antigen inhalation, continuous intravenous infusion of nicardipine 7 $\mu\text{g}/\text{kg}/\text{min}$ depressed the open airway pressure by about 60% compared with the saline-treated group. Inhibition of mean pulmonary resistance (R_L) was about 50% and that of the inverted value of dynamic compliance ($1/\text{C}_\text{dyn}$) about 36%. However, the same concentration of nicardipine did not significantly affect the airway response in the asthmatic model induced by the inhalation of leukotriene C_4 . These results suggest that nicardipine, at the concentration used in the present study, did not block the direct effect of SRS-A on the smooth muscle, but blocked the Ca^{2+} influx required for the synthesis of SRS-A and its release.

Key words: SRS-A; leukotriene C_4 ; Ca^{2+} -antagonist; nicardipine.

Accepted for publication 27 November 1984

Slow reacting substances of anaphylaxis (SRS-A), an important chemical mediator of bronchial asthma, is synthesized from arachidonic acid and is considered to be a compound of leukotriene C_4 (LTC_4) and leukotriene D_4 (LTD_4). Ca^{2+} is required in the process of its synthesis and release. We have already reported that nifedipine, a Ca^{2+} antagonist, inhibited the synthesis and release of SRS-A and that nifedipine also inhibited the tracheal response to LTC_4 (2). The present study reports on the effect of another Ca^{2+} antagonist, nicardipine, which we found to differ in some respects from nifedipine.

METHODS

The study was performed with 26 Hartley strain male guinea pigs (body weight 340–370 g) divided into four groups.

Experiment 1

The guinea pigs were passively sensitized with i.v. injection of 0.5 ml ovalbumin (OA) anti-serum (4 h PCA value, 12,800 times) 20–30 h previously, and anesthetized with 45 mg/kg of pentobarbital (Nembutal®). According to the method of Fujimura (1), and to avoid histamine-induced bronchoconstriction, diphen-

hydramine HCl 20 mg/kg was injected intraperitoneally 15 min before the inhalation of 2 mg/ml OA, which was given for 30 sec by the quantitative ultrasonic nebulizer for small animals (3). In the test group ($n = 6$), 10 min before OA inhalation, nicardipine was continuously infused i.v. at the speed of 7 $\mu\text{g/kg/min}$ for 40 min. In the control group ($n = 6$), the same amount of physiological saline was infused.

Experiment 2

While 0.1 $\mu\text{g/ml}$ of LTC_4 was inhaled for 30 sec with the nebulizer for small animals, the same infusions of nicardipine ($n = 7$) and physiological saline in the control group ($n = 7$) were performed continuously as in Experiment 1.

In these experiments, open airway pressure (P_{ao}) was measured, and, in order to evaluate the changes in the peripheral and proximal airways separately, dynamic compliance of the lung (C_{dyn}) and mean pulmonary resistance (R_L) were measured by the body plethysmograph for small animals (2). Time courses of the changes in P_{ao} for 30 min were expressed as percentage of the control value at starting (i.e. immediately before the inhalation).

Statistical analysis was made by Mann-Whitney's U-test; differences with $P < 0.05$ were judged to be statistically significant.

RESULTS

Airway response to antigen (OA)-inhalation

As shown in Fig. 1, P_{ao} reached the maximum value of $188 \pm 38\%$ 10 min after OA inhalation in the saline-treated group, whereas in the nicardipine-treated group the maximum value 10 min after OA inhalation was $106 \pm 46\%$ ($P < 0.05$). 5 min after the OA inhalation the increase in P_{ao} was significantly inhibited by nicardipine throughout the entire course.

Airway response to LTC_4 -inhalation

As shown in Fig. 2, P_{ao} , 5 min after LTC_4 inhalation reached maximum values of $146 \pm$

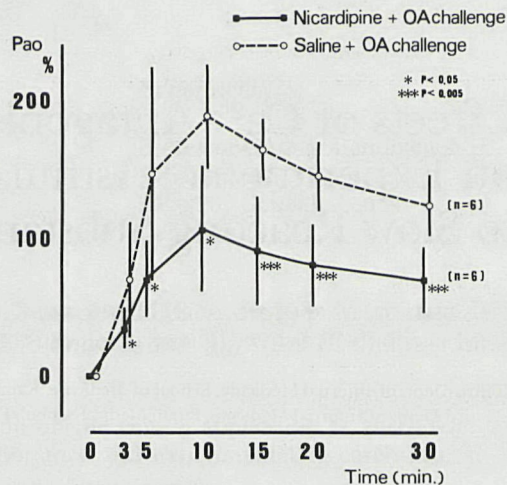


Fig. 1. Percent increase of open airway pressure (P_{ao}) after OA challenge in passively immunized guinea pigs. (■—■): nicardipine-infused group ($n = 6$) and (○—○): saline-infused group ($n = 6$). Each value represents mean $\pm$ SD.

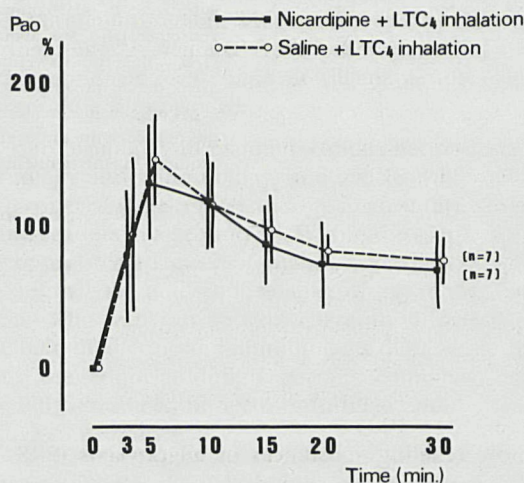


Fig. 2. Percent increase of open airway pressure (P_{ao}) after leukotriene C_4 inhalation. (■—■): nicardipine-infused group ($n = 7$) and (○—○): saline-infused group ($n = 7$). Each value represents mean $\pm$ SD.

33% and $130 \pm 40\%$ in the saline-treated ($n = 7$) and nicardipine-treated ($n = 7$) groups respectively, thus showing no significant difference. There was also no significant difference between the two groups throughout the entire course.

Table 1
Percent increase of maximum $1/C_{\text{dyn}}$ and R_L

	Saline group	Nicardipine group	
OA challenge			
$1/C_{\text{dyn}}$	240 ± 42	117 ± 54	$P < 0.05$
R_L	128 ± 44	64 ± 10	$P < 0.005$
LTC ₄ inhalation			
$1/C_{\text{dyn}}$	158 ± 23	156 ± 50	n.s.
R_L	115 ± 38	100 ± 22	n.s.

Each value represents mean $\pm$ SD.

Separate evaluation of changes in the peripheral and proximal airways

C_{dyn} and R_L were measured by the method described above, and, in order to compare the ratio of their changes, the inverted value of C_{dyn} , $1/C_{\text{dyn}}$, was calculated. Maximum changes in P_{ao} were obtained after 10 min in the antigen inhalation experiment and after 5 min with LTC₄. Therefore, the percentage values of $1/C_{\text{dyn}}$ at these times were compared with the percentage values of R_L at corresponding times. As shown in Table 1, in the OA inhalation experiments, $1/C_{\text{dyn}}$ was $240 \pm 42\%$ in the saline-treated group and $117 \pm 54\%$ in the nicardipine-treated group; thus, nicardipine markedly inhibited the change of $1/C_{\text{dyn}}$ % in the OA inhalation experiment. The change in R_L % was also markedly depressed by nicardipine, i.e., $128 \pm 44\%$ in the saline-treated group and $64 \pm 10\%$ in the nicardipine-treated. However, in the LTC₄ inhalation experiments, as shown in Table 1, percentage differences in $1/C_{\text{dyn}}$ and R_L between the control group and the nicardipine-treated group were not statistically significant.

DISCUSSION AND CONCLUSION

Nicardipine is a Ca^{2+} antagonist discovered by Takenaka et al. (4), and is known to have a dilatory effect on the peripheral and brain blood vessels (5). However, until recently, there have been few reports on its airway dilating

effects and, especially, its anti-asthmatic effects. In our present study, continuous administration of $7 \mu\text{g/kg/min}$ of nicardipine significantly inhibited the changes in P_{ao} %, $1/C_{\text{dyn}}$ % and R_L % in the experimental asthma mediated by endogenous SRS-A invoked by antigen inhalation, whereas it did not inhibit these values in the experimental asthma produced by LTC₄ inhalation. These results suggest that nicardipine did not block the direct effect of SRS-A on the airway smooth muscle, but blocked the Ca^{2+} inflow required for the synthesis of SRS-A from arachidonic acid and its release. In this respect, nicardipine differs from nifedipine, which, as we have reported, inhibits the direct effect of SRS-A on the airway smooth muscle (1). In addition, the clinical i.v. dose of $1\text{--}10 \mu\text{g/kg}$ nicardipine used to obtain vasodilation of the brain (5), is almost similar to the dose used in the present study; thus, nicardipine is expected to have therapeutic effect on human asthma.

REFERENCES

1. Fujimura, M.: Inhibitory effects of steroids on slow-reacting substance of anaphylaxis (SRS-A) mediated bronchoconstriction in the guinea pig in vivo. - Evaluation with inhalation of antigen and leukotriene C₄. (In Japanese). *Jpn. J. Allergol.* 32, 365-375, 1983.
2. Koshino, T., Fujimura, M., Minami, S., et al.: The inhibitory effect on SRS-A mediated bronchoconstriction in the guinea pig by Ca^{2+} antagonist, nifedipine. (In Japanese). *Igaku no Ayumi* 127, 107-108, 1983.
3. Minami, S., Okafuji, K., Saga, T., et al.: A new quantitative inhalation apparatus for small animals. (In Japanese). *Jpn. J. Thorac. Dis.* 21, 252-258, 1983.
4. Takenaka, T., Usuda, S., Nomura, T., Maeno, H. & Sado, T.: Vasodilator profile of a new 1,4-dihydropyridine derivative, 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylic acid 3-(2-(N-benzyl-N-methylamino)) ethyl ester 5-methyl ester hydrochloride (YC-93). *Arzneim. Forsch.* 2, 2172-2178, 1976.
5. Takenaka, T. & Handa, J.: Cerebrovascular effects of YC-93, a new vasodilator, in dogs, monkeys and human patients. *Int. J. Clin. Pharmacol. Biopharm.* 17, 1-11, 1979.

Address:

Takeshi Koshino, M.D.
Third Dept. of Medicine
Kanazawa Univ. School of Med.
13-1, Takara-machi
Kanazawa 920
Japan

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.