No Adverse Effect of Non-Steroidal Anti-Inflammatory Drugs, Sulindac and Diclofenac Sodium, on Blood Pressure Control with a Calcium Antagonist, Nifedipine, in Elderly Hypertensive Patients

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TAKEUCHI, K., ABE, K., YASUJIMA, M., SATO, M., TANNO, M., SATO, K. and YOSHINAGA, K. No Adverse Effect of Non-Steroidal Anti-Inflammatory Drugs, Sulindac and Diclofenac Sodium, on Blood Pressure Control with a Calcium Antagonist, Nifedipine, in Elderly Hypertensive Patients. Tohoku J. Exp. Med., 1991, 165 (3), 201-208 —— Effect of non-steroidal anti-inflammatory drug (NSAID) on blood pressure (BP) control was evaluated in elderly hypertensive patients treated with calcium antagonist. The study was based on a randomized, crossover design to compare the effect of an NSAID, sulindac, with that of another NSAID, diclofenac sodium, in the hypertension treatment. The study was completed in six elderly female subjects (the average age: 66±3 year) whose systolic BP and diastolic BP were more than 160 mmHg and more than 95 mmHg, respectively. When BP was controlled by nifedipine (20 mg x 2 per day in slow releasing form) within normal limits, sulindac (100 mg x 3 per day) or diclofenac sodium (25 mg x 3 per day) was administered for a week. After one week-washout period, the other NSAID was substituted. Plasma and urinary variables were measured on the final day of each study period. The average systolic BP and diastolic BP and the entry of study were 167±5 mmHg and 93±5 mmHg, respectively.

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Abbreviations: NSAID, non-steroidal anti-inflammatory drug; PG, prostaglandin; BP, blood pressure; Ca, calcium.
Nifedipine significantly decreased the systolic BP to 140±4 mmHg (p < 0.02) and the diastolic BP to 84±4 mmHg (p < 0.05). Addition of either sulindac or diclofenac sodium did not affect BP, whereas urinary PGE₂ excretion and plasma renin activity were significantly inhibited. Plasma creatinine and electrolyte concentration were not changed by the NSAIDs. The results indicate that either sulindac or diclofenac sodium does not interfere with control of hypertension by a calcium antagonist, nifedipine in elderly hypertensive patients. And, it is suggested that renal PGEs does not play an evident role in BP control with nifedipine.

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of chronic degenerative joint diseases and musculoskeletal pain, which are commonly observed in elderly people. Hypertension is also a disease frequently observed in the elderly. Therefore, the potential for concurrent administration of NSAIDs and antihypertensive drugs is considerable, especially in the elderly. Recently, more attentions have been paid on the adverse effect of NSAIDs in the treatment of hypertension, because the action of antihypertensive drugs may be blocked by certain NSAIDs (Oates 1990). It has been reported that NSAIDs interfered the antihypertensive effects of diuretics (Wong et al. 1986; Radack et al. 1987), β-blockers (Wong et al. 1986; Baez et al. 1987), and angiotensin converting enzyme inhibitors (Salvetti et al. 1982).

Antihypertensive effect of a calcium (Ca) antagonist, verapamil, has been shown to be inhibited by additional administration of aspirin, but to be unaffected by piroxicam (Das 1982; Baez et al. 1987). Moreover, the antihypertensive effect of nifedipine was not affected by indomethacin (Salvetti et al. 1986). Thus, the effect of NSAIDs on the hypertension treatment with Ca antagonist appears to be controversial. Hence, more careful evaluation about the effect of NSAIDs on BP control is required. On the other hand, sulindac is shown to have a rare side effect on renal function (Bunning and Barth 1982; Ciabattoni et al. 1984; Sedor et al. 1984). It may also be probable that sulindac has no adverse affect on hypertension treatment that favors renal function. The aim of the present study is, therefore, to examine the effect of an NSAID, sulindac on hypertension control with nifedipine, comparing to the effect of diclofenac sodium, another frequently used NSAID, in order to assess the safety of NSAID administration during antihypertensive treatment in the elderly hypertensive patients.

**METHODS**

**Subjects**

Nine female elderly hypertensive patients entered the study. They were hospitalized in Hanamaki Hospital, Hanamaki; Tohno Prefectual Hospital, Tohno, or Takada Prefectual Hospital, Rikuzen-Takada, from March 1987 to October 1987. All the subjects were patients with essential hypertension. The subjects were selected when their systolic...
BP or diastolic BP maintained at more than 160 mmHg or at 95 mmHg, respectively, at the baseline period. Three out of the nine subjects, however, failed to complete the study protocol and were excluded from the study group, because they did not strictly observe salt-restriction, urine collection or drug intake. The average age of the six subjects who completed the study was 66±3 year (ranging from 59 to 74 year). The average of height and weight were 149±2 cm and 56.7±3.9 kg, respectively. In order to evaluate the role of renal prostaglandin (PG) by measuring urinary PG excretion, only female subjects were chosen, since the measurement of urinary PG in male is problematic because of the interference of PG originated from seminal fluid (Sato et al. 1983; Patrono and Dunn 1987). They were either previously untreated or currently treated with antihypertensive drugs. If treated, the drug was discontinued at least 2 weeks before entry into the study. They also suffered from chronic degenerative joint disease and had experienced NSAID therapy before admission. These subjects had never had either edema or proteinuria indicating a renal disease. The optic fundoscopy examination showed mild hypertensive changes in all subjects. The severity of hypertension of the subjects fell in the classification of WHO, grade I.

Study protocol

In the study, salt intake was restricted to 7 g NaCl per day. The study was based on a randomized, crossover design. After 2 week baseline period, nifedipine (slow releasing form, 20 mg×2 per day) was administered. When systolic BP and diastolic BP decreased to less than 160 mmHg and 95 mmHg, respectively, sulindac (100 mg×3 per day) or diclofenac sodium (25 mg×3 per day) was concomittently administered for a week. Then, after one-week washout period, another NSAID was substituted. On the final day of each period (baseline, nifedipine alone, nifedipine plus sulindac or nifedipine plus diclofenac sodium), BP, laboratory data of plasma and urine (listed in Table 1) were measured and the average of them was compared to analyse the difference. Before entry into the study, informed consent was obtained.

BP was measured by a standard sphygmomanometer after 10 min recumbency. Each time, BP was measured three times and the average of the last two BP measurements was calculated to obtain the BP at the time. BP measurements were performed four times daily (06 : 00; 10 : 00; 16 : 00; 21 : 00). The average of all BP measurements in each period was calculated to represent BP of the period.

All the urinary and plasma samples were collected in our laboratory. Urinary PGE$_2$ was measured by a modification of the method established in our laboratory (Abe et al. 1978; Sato et al. 1983). Briefly, 1 ml of urine sample was acidified by hydroxychloride to pH 3.0 and PG was extracted by ethylacetate. The extract was then lyophilized at 37°C. The sample was dissolved in acetone (1 ml) and lyophilized, again. The lyophilized sample was dissolved in 0.2 ml of solvent I (toluene : ethyl acetate : methanol =60 : 40 : 10) and then filled up to 1.0 ml with solvent M (toluene : ethyl acetate =60 : 40). To purify PGE$_2$, the sample was then applied to silicic acid column chromatography. After washing the column with solvent II, the sample (1 ml) was applied. Then, to elute PGA and PGB, 5 ml of solvent II was applied to the column and the eluted solution was discarded. To elute PGE and PGF, 5 ml of solvent I (toluene : ethyl acetate : methanol =60 : 40 : 20) was next applied and the eluted solution was saved, lyophilized and stored at -20°C until future PGE$_2$ measurement by radioimmunoassay (RIA). Recovery rate of PGE$_2$ was estimated to be 60%. In RIA, the sample was dissolved in phosphate buffered solution. RIA was performed using a highly specific antibody against PGE$_2$ obtained from Pasteur Institute, Paris, France and tritiated PGE$_2$ from New England Nuclear, Boston, MA, USA. The lower limit of PG determination was 3 pg/ml. Plasma renin activity (PRA) was measured by the method of Abe et al. (1975). The normal range is 5-30 ng angiotensin 1/ml/6 hr. Plasma aldosterone concentration (PAC) was measured by a commercially available kit (Dinabot, Tokyo). The normal range of PAC is 2-12 ng/100 ml. Plasma creatinine (Cr),
plasma and urinary sodium, plasma and urinary potassium were measured by their standardized methods. All values are expressed as mean±s.e. Statistical analysis was performed by a two-tailed, paired t-test. p<0.05 was considered to be significant.

RESULTS

The systolic or diastolic BP in the baseline period was 167±5 mmHg or 93±

![Graph showing the effects of sulindac and diclofenac sodium on blood pressure control in elderly hypertensive patients treated with nifedipine. Changes of blood pressure (BP) in six individual subjects are indicated. The subjects were treated with nifedipine and NSAIDS (diclofenac sodium or sulindac) as described under “methods”. Upper and lower panels systolic BP and diastolic BP, respectively. Date of the same patients are dipicted by numbers 1 to 6 in each panel. Each value indicates the average of all BP measurements during each study period. Statistical analysis was performed using a two-tailed, paired t-test. n.s., not significant.](image-url)
As shown in Fig. 1, nifedipine significantly decreased systolic BP and diastolic BP within normal limits (systolic BP: 140±4 mmHg, p <0.02; diastolic BP: 84±4 mmHg, p <0.05). Addition of either sulindac or diclofenac sodium did not affect the BP levels obtained by nifedipine.

Table 1 summarizes the changes in laboratory data of blood and urine examined in this study. Nifedipine significantly increased PRA, while it did not significantly affect the other variables. Addition of sulindac as well as diclofenac sodium significantly decreased urinary prostaglandin excretion and PRA. Although no significant statistical difference was obtained, daily urinary sodium and potassium excretion as well as urine volume had a tendency to decrease in response to either sulindac or diclofenac sodium. The other variables were not changed by either of the NSAIDs. There was no significant difference between the effect of sulindac and that of diclofenac sodium.

**DISCUSSIONS**

Ca antagonist is a potent vasodilator. Recently, Ca antagonist has been recommended to be used as one of the first choice antihypertensive drugs in elderly hypertensive patients (Buhler et al. 1984; Ben-Ishay et al. 1986; The 1988 Joint National Committee 1988). In the present study, BP was well controlled by nifedipine alone in the elderly hypertensive patients. The result, therefore, supports the efficacy of Ca antagonist as a drug for hypertension monotherapy.
Nifedipine also did not affect renal as well as plasma variables except PRA. The PRA increase is predictable because Ca antagonist has been shown to increase renin release from the kidney (Loutzenhiser and Epstein 1985; Kurtz 1989). However, despite of the increase in PRA (which causes an increased synthesis of a vasoconstrictive hormone, angiotensin II), BP was controlled well during the nifedipine treatment. It is suggested that the increased angiotensin II synthesis does not affect the BP control with nifedipine, since vasodilatory effect of nifedipine is considerable.

Sulindac did not affect the control of hypertension by Ca antagonist, consistent with the previous reports (Salvetti et al. 1986; Baez et al. 1987). Diclofenac sodium also did not interfered with the BP control. The effectiveness of these NSAIDs in the subjects was confirmed by the inhibition of urinary PGE₂ excretion, because these NSAIDs have been shown to be inhibitors against PG synthesis (Roberts et al. 1985; Vriesendorf et al. 1986). The result indicates that sulindac as well as diclofenac sodium does not interfere with BP control obtained by nifedipine, despite of reduced renal PGE₂ synthesis. On the other hand, sulindac has been shown to be a renal sparing drug (Bunning and Barth 1982; Sedor et al. 1984; Ciabattoni et al. 1984). The rare adverse effect of sulindac on renal function is due to less inhibition of renal PG synthesis, although the inhibitory effect of sulindac on renal PG synthesis is still controversial (Patrono and Dunn 1987; Stillman and Schlesinger 1990). In the present study, we measured urinary PGE₂ excretion, which reflects renal medullary PGE₂ synthesis. The results have shown that sulindac as well as diclofenac sodium significantly inhibited PGE₂ excretion during nifedipine treatment. It indicates that renal PGE₂ plays a marginal role, if any, in the BP control of hypertension by Ca antagonist. None the less, it might be noted that renal PGE₂ plays a role in an acute (2 hr) natriuretic effect of nifedipine (Tsunoda et al. 1986).

The present study has showed that sulindac and diclofenac sodium decreased PRA. Renin release is known to be preferentially influenced by sodium and volume status in the body (Keeton and Campbell 1981). Therefore, when PRA is considered to be an indicator for the volume balance, our observations may be explained as follows: Ca antagonist increased renal as well as systemic vessel capacity because of vasodilation, causing a relative volume loss and a reduced renal perfusion pressure, which, in turn, stimulated renin release (as evaluated by an increase in PRA). Addition of NSAIDs inhibited renal diuretic and natriuretic PGE₂ synthesis, followed by an increase in plasma volume resulting in inhibition of renin release. Although there was no significant change, the tendency of NSAID responsiveness to daily sodium and urine output may support this explanation. However, in such a circumstance, since the vasodilatory effect of Ca antagonist is considerable, there seems to be no obvious effect of PGE₂ inhibition on either renal function or blood pressure control.

Thus, we have indicated that no adverse effect of NSAIDs, sulindac and
diclofenac sodium, on BP control with nifedipine. It has already been reported that, distinct from other NSAIDs, sulindac did not interfere with the efficacy of hypertension treatment with diuretics, β-blockers and angiotensin converting enzyme inhibitors (Salvetti et al. 1982; Steiness and Waldorf 1982; Puddy et al. 1985; Lewis et al. 1986; Baez et al. 1987). It has also been reported that sulindac did not affect the control of hypertension by verapamil (Baez et al. 1987). Taken together, it is indicated that sulindac can be used more safely than other NSAIDs during the treatment of hypertension with antihypertensive group, including Ca antagonist. In addition, as shown in the present study, sulindac may be used with safety even in the elderly patients in salt-restriction. Moreover, diclofenac sodium may also be used with the same safety as sulindac. The observation, however, does not suggest to neglect a careful laboratory examination during NSAID treatment. And, more clinical studies would be required to further establish the safety of NSAIDs in hypertension treatment with Ca antagonist.

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References


