EFFECTS OF DILTIAZEM HYDROCHLORIDE ON
RENAL HEMODYNAMICS AND
URINARY ELECTROLYTE EXCRETION

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MASAKAZU MOMOMURA*, GOH TOMONAGA AND TSUNE HOSHINO

Diltiazem hydrochloride, a potent coronary dilator, was administered in 18
patients to evaluate its effect on renal hemodynamics and urinary electrolyte
excretion.

Renal blood flow (RBF), glomerular filtration rate (GFR), and cardiac
output were determined in 8 ambulatory patients by means of external
counting of radioisotope dilution before and 3 or 4 weeks after the medica-
tion.

Although RBF tended to increase after the therapy, there was no statisti-
cally significant change in RBF, GFR and cardiac output. Renal fraction of
cardiac output (RBF/CO) showed a significant increase by 29.5% after the
therapy, indicating that the renal vascular resistance decreased to a greater
extent than the extrarenal vascular resistance.

Standard renal clearance was performed in 10 inpatients whom 60 mg of
diltiazem was administered orally. Renal plasma flow (RPF) showed an
average increase by 15% 3 hr after the administration of the drug, which was
not, however, statistically significant. There was no certain trend for GFR
and filtration fraction. Urinary sodium excretion (U_{Na} V) began to increase
one hr and reached its peak 2 hr after the medication in 9 out of the 10
patients.

It may be concluded that diltiazem has a direct inhibitory action against
the renal tubular reabsorption of sodium, although the participation of renal
hemodynamics can not be denied.

The coronary vasodilator action of a 1, 5-
benzothiazepine derivative “Diltiazem
hydrochloride” (diltiazem) synthesized by Kugita
et al. has been investigated extensively by Sato
et al and Nagao et al. The drug exerts vasodi-
lator actions on not only coronary arteries but
also femoral, carotid and renal arteries of dogs.
However, there are different reports concerning
the effect of diltiazem on blood vessels and func-
tions of human kidney. Diltiazem given orally to patients with angina pectoris causes a
decrease in cardiac output. In this sense, renal
arterial resistance and fraction of cardiac output
to renal blood flow should be determined in elu-
cidation of the effect of diltiazem on the renal
blood vessel because there exists a possibility

Key Words:
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Renal clearance
Precordial dilution curve

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that the vasodilator action of the drug on renal vessels is masked by its action of reducing cardiac output.

In the present work the action of diltiazem on blood vessels of human kidney was investigated non-invasively by extracorporeal determination of cardiac output and renal blood flow using radionuclides. The diuretic and natriuretic actions of the drug were additionally examined by measuring the renal clearance and urinary sodium excretion rate before and for three hours' duration after oral administration of the drug.

SUBJECTS AND METHODS

I. Renal vasodilator action

The method of extracorporeal determination for cardiac output (CO) by radioangiography has been described in our previous report. About 20 μc of 131I-human serum albumin was injected into the peripheral vein. Scintillation detector containing a 1.5 × 1.0" sodium iodide crystal was collimated along the left sternal margin in the third intercostal space and the dilution curve of radioactivity was recorded on pen-writing paper. Blood sample was drawn from the contralateral vein 7 min later to correct the extracorporeally measured value. CO was calculated by the following equation.

\[
CO = \frac{\text{Dose of RI}}{\text{Blood RI level 7 min after injection}} \times \frac{\text{Area below initial circulation dilution curve}}{\text{Extracorporeally measured value}}
\]

Renal plasma flow (RPF) and glomerular filtration rate (GFR) were measured by single i.v. injection and single blood collection method. 131I-Hippuran and 131I-iothalamate were used as the tracers for determining RPF and GFR respectively. After injecting these RI substances intravenously, disappearance curves for RPF and GFR were continuously recorded by pointing the scintillation detector to the sternal center of the second intercostal space, by measuring for 30 min and by measuring for 60 min respectively. In order to balance the extracorporeally measured value, the blood samples for RPF and GFR were drawn 15 and 30 min after the start of the measurement respectively.

\[
\text{RPF or GFR} = \frac{\text{Dose of RI}}{\text{Cto}} \times \frac{0.693}{t^{\frac{1}{2}}}
\]

where Cto: Concentration of RI substance in the blood when disappearance curve is interpolated in 0 hr.

t^{\frac{1}{2}}: Half time when disappearance curve is approximated by 1 compartment model.

Eight ambulatory patients to the Department of Cardiology, Tenri Hospital comprised the experimental subjects. The patients ranged in age from 41 to 76 with an average of 54.9.

Four, two and two patients suffered from angina of effort, old myocardial infarction and painless ischemic heart disease respectively. CO, RPF and GFR were measured in these patients during three days by altering the date of measurement, and subsequently the patients were started on diltiazem therapy, 90 mg per day, for 3 or 4 weeks. After the end of the therapy, CO, RPF and GFR were measured again. Renal arterial resistance (RAR) was calculated by the following formula.

\[
\text{RAR} = \frac{\text{Mean blood pressure} \times 1332}{\text{RPF} \times (1 - \text{hematocrit})} \times \text{dynes} \cdot \text{sec} \cdot \text{cm}^{-5}
\]

Mean blood pressure was assumed to be a sum to a half of pulse pressure of brachial arterial pressure (measured by Riva Rocci sythymonometer) and diastolic pressure.

II. Renal clearance and natriuretic action

Renal clearance was examined by the standard renal clearance test. The concentration of sodium thiosulfate and para-aminobiphenic acid (PAH) in the blood were kept constant by drip infusion. The test was carried out in a resting recumbent position under a morning fasting condition. Medications other than digitalis therapy were discontinued on the day of test. Water, 500 ml, was given orally at 8:00 a.m. by taking for 15 min and subsequently 50 ml of 5% glucose containing 1.5 g of sodium thiou sulphate and 0.75 g of PAH was given by intravenous injection at 8:30 a.m. by taking for 10 min. Thereafter 5% glucose containing 4.6% sodium thiou sulphate and 1.5% PAH was infused continuously at a rate of 1 to 1.5 ml/min. The urinary bladder was emptied at 9:00 a.m. and thereafter the urine was collected at 30-min intervals, while blood samples were collected at the intermediary time. Blood and


<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Age &amp; Sex</th>
<th>Diagnosis</th>
<th>mBP (mmHg)</th>
<th>RPF (ml/min)</th>
<th>RBF (ml/min)</th>
<th>GFR (ml/min)</th>
<th>FF</th>
<th>RAR (dynes. sec. cm⁻²)</th>
<th>CO (ml/min)</th>
<th>RBF/CO (%)</th>
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* p < 0.05
mBP=Mean blood pressure; RPF=Renal plasma flow; RBF=Renal blood flow; GFR=Glomerular filtration rate; FF=Filtration fraction; RAR=Renal arterial resistance; CO=Cardiac output; EA=Effort angina; MI=Myocardial infarction; B=Before; A=After

Urine specimens were collected repeatedly for 4 hours' duration until 1:00 p.m. Diltiazem in a dose of 30 to 60 mg was given orally at 10:00 a.m., i.e., there was a 1-hr control time before the administration of diltiazem and the course was observed for 3 hr after the medication. Concentrations of sodium and potassium in the plasma and urine were determined by flame photometer. Osmotic pressure was measured by Fiske osmometer. Sodium thiosulfate and PAH in the plasma and urine were determined by Brun's method.13

The inpatients in the Department of Cardiology, Tenri Hospital served as the experimental subjects who received a sodium intake of 120 mEq per day. They suffered from chronic congestive heart failure(6) and essential hypertension(1) and one of them was in postoperative course of renovascular hypertension and two of them were after cure of beriberi. These subjects ranged in age from 20 to 62 with an average of 46.2.

Statistical analysis of the data was performed using Student's paired t-test. All results are expressed as the mean ± 1 standard deviation.

RESULT

I. Renal vasodilator action

Table I represents renal hemodynamics, CO and RBF/CO in 8 patients before and after oral administration of diltiazem.

RPF increased in 5 and decreased in 3 cases after the medication. There was an increase in RPF by 9.8% after the therapy, which was not however statistically significant.

The change in RBF was similar to that in RPF, showing an increase by 12.8%. The increased value after the therapy was not statistically different from the value before the therapy.

TABLE II  PULSE RATE, BLOOD PRESSURE AND SERUM DOSIUM/POTASSIUM RATIO BEFORE AFTER THE ADMINISTRATION OF DILTIAZEM

<table>
<thead>
<tr>
<th></th>
<th>Pulse rate (beat/min)</th>
<th>Blood pressure (Ps/Pd) (mmHg)</th>
<th>Serum Na/K (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>61 ± 10</td>
<td>103 ± 18/63 ± 10</td>
<td>138 ± 1/4.4 ± 0.3</td>
</tr>
<tr>
<td>3 hr</td>
<td>64 ± 12</td>
<td>106 ± 14/62 ± 7</td>
<td>139 ± 2/4.2 ± 3.9</td>
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</table>

Mean ± SD; Ps=Systolic pressure; Pd=Diastolic pressure

GFR increased and decreased in 4 cases each respectively after the therapy, in which there existed no certain tendency.

Filtration fraction(FF) increased and decreased 2 and 6 cases respectively, which tended to decrease after the medication. The decrease in the value after the medication was not statistically different from the pretherapeutic value.

RAR was measured in only 7 patients, which increased and decreased in 2 and 5 patients respectively after the medication. Although the value showed a decrease by 15%, there were no significant differences in the values before and after the medication.

Only one out of 7 patients whose CO was measured showed an increase in CO after the therapy, while the remaining 6 patients showed a decrease in the value. Although CO showed the average decrease by 20%, there existed no significant differences before and after the therapy.

On the other hand, RBF/CO increased in all 7 patients after the therapy. There was the average increase by 25.5% after the medication, which was statistically high at 5% level of significance.

II. Renal clearance and urinary electrolyte excretion

Table II lists pulse rate, blood pressure and both of serum sodium and potassium levels before and after the administration of diltiazem.

1. Pulse rate
   There was no definite tendency for change in pulse rate. Measurement of the value after the medication was impossible in the 3 patients.

2. Blood pressure
   The average of blood pressure before the medication was 103/63 mmHg, indicating that all patients were not hypertensive. The posttherapeutic average was 106/62 mmHg, which was similar to the pretherapeutic value.

3. Serum electrolyte levels
   Concentrations of Na and K in the serum before the therapy were within normal range. There was no significant change after the medication.

Renal hemodynamics, urinary sodium and potassium excretion before and after diltiazem therapy are summarized in Table III.

4. RPF
   RPF tended to increase after the therapy in 7 out of the 10 patients except 3 patients who showed decrease in RPF. Though there was an average increase by 15% 3 hr after the medication in RPF, the increase was not statistically significant.

5. GFR
   There was no certain trend after the therapy, i.e., GFR increased, unchanged and decreased in 5, 3 and 2 patients respectively. The average value increased slightly, but such was not statistically significant.

6. FF
   There were no appreciable changes in FF before and after the therapy. The change did not show any significant difference.

7. Urinary sodium excretion(U_{NaV})
   The U_{NaV} increased even 1 hr after the therapy in 7 out of the 10 patients and reached its peak 2 hr after the medication in 9 out of 10 patients. There was an average increase in U_{NaV} by 46.4% 2 hr after the medication. The increased value 3 hr after the therapy was slightly lower than that 2 hr after the therapy in 6 cases, which was still 45.0% increase in U_{NaV} as compared with the premedication value.

8. Urinary potassium excretion (U_{KV})
   There was no significant change in U_{KV} after the therapy, although the average postmedication value increased by 25%.

9. Percentile reabsorption of renal tubular Na(T_{Na})
   T_{Na} gradually decreased after the therapy, i.e., the value before the therapy was 98.2% in average and the value became 97.7% 2 hr after

Effects of Diltiazem on Renal Hemodynamics

<table>
<thead>
<tr>
<th>TABLE III</th>
<th>RENAL HEMODYNAMICS, ELECTROLYTE EXCRETION, AND OSMOLAR CLEARANCE BEFORE AND AFTER THE ADMINISTRATION OF DILTIAZEM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CH_{2}O (ml/min)</td>
</tr>
<tr>
<td>Control</td>
<td>392 ± 173</td>
</tr>
<tr>
<td>1 hr</td>
<td>392 ± 173</td>
</tr>
<tr>
<td>2 hr</td>
<td>392 ± 173</td>
</tr>
<tr>
<td>3 hr</td>
<td>392 ± 173</td>
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</table>

*P < 0.05; **P < 0.01; Mean ± SD

Diltiazem, synthesized as a potent coronary vasodilator drug, elicits an increase in coronary blood flow without causing an increase in myocardial oxygen consumption. The drug also simultaneously induces dilation of the femoral artery, but the femoral vasodilator activity of the drug is reported to be one-fourth of the coronary vasodilator activity. Yamaguchi et al. have extended the study of the drug efficacy on the artery and function of dog kidney. According to the experimental result, the systemic administration of diltiazem or the injection of the drug into the renal artery produces the augmentation of the renal blood flow, increase in urine volume and augmentation of natriuresis and meanwhile the drug antagonizes the renal vasoconstrictor action of angiotensin. On the other hand, the effect of orally given diltiazem on human kidney has been reported differently. Sakurai et al. described that RBF was increased in 6 out of 8 patients after the oral administration of the drug, while there were no certain tendency to the changes in UV and UNaV. In the present study RBF was not always increased after the oral administration diltiazem. Although results of human experiments do not always agree with those of animal experiments, oral diltiazem caused a light decrease in CO in man. It is quite possible that the renal vasodilator action of diltiazem is counteracted by its the therapy (P < 0.05). The value 3 hr after the therapy showed an average decrease by 1% which was not statistically significant.

10 Urine volume (UV)

UV gradually decreased after the therapy. The decrease in UV would be a time-course change due to water given for the diuretic purpose just before measurement of renal clearance rather than be attributed to the effect of diltiazem.

11 Osmolar clearance (Cosm)

Cosm increased gradually to reach the peak between 1 and 2 hr after the therapy followed by slight decrease between 2 and 3 hr after the therapy. However, the increase in Cosm was not statistically significant.

12 Free water clearance (CH_{2}O)

The degree of negative value of CH_{2}O increased in parallel to the elapse of time after the therapy. Increased water reabsorption due to slightly dehydrated state during the test would underlie an increase in negative value, rather than the effect of diltiazem.

DISCUSSION

Diltiazem, synthesized as a potent coronary vasodilator drug, elicits an increase in coronary blood flow without causing an increase in myocardial oxygen consumption. The drug also simultaneously induces dilation of the femoral artery, but the femoral vasodilator activity of the drug is reported to be one-fourth of the coronary vasodilator activity. Yamaguchi et al. have extended the study of the drug efficacy on the artery and function of dog kidney. According to the experimental result, the systemic administration of diltiazem or the injection of the drug into the renal artery produces the augmentation of the renal blood flow, increase in urine volume and augmentation of natriuresis and meanwhile the drug antagonizes the renal vasoconstrictor action of angiotensin. On the other hand, the effect of orally given diltiazem on human kidney has been reported differently. Sakurai et al. described that RBF was increased in 6 out of 8 patients after the oral administration of the drug, while there were no certain tendency to the changes in UV and UNaV. In the present study RBF was not always increased after the oral administration diltiazem. Although results of human experiments do not always agree with those of animal experiments, oral diltiazem caused a light decrease in CO in man. It is quite possible that the renal vasodilator action of diltiazem is counteracted by its
action of decreasing CO, resulting in no increase of renal blood flow.

Therefore, measurement of RAR and RBF/CO is necessary for examination of the action of diltiazem on the renal blood vessel. CO, RBF and GFR can be examined repeatedly in a same patient by extracorporeal measurement using R11,12 and hence the method is excellent for evaluation of drug efficacy like diltiazem. RBF was not significantly increased after oral administration of diltiazem when examined by this method, but the distribution rate of the blood to the kidney (RBF/CO) was increased significantly while the average value of RAR was decreased alike after the drug. However, due probably to the paucity of patients observed in this work, the action of the drug was not statistically significant. Sato et al. demonstrated that at the dose level which can augment the coronary blood flow by 100%, diltiazem could induce the increases in femoral, carotid and renal arterial flows by 25%, 30% and 10% respectively.3

Because the action of diltiazem on the renal artery is one-tenth of that on the coronary artery, such assumption that ordinary oral dose of the drug cannot significantly increase RBF may not be denied. It seems likely that the change in distribution of the systemic blood flow by the action of diltiazem leads to increases in blood flow in the cardiac, renal and femoral arterial areas, which ultimately results in decreased blood flow in some other regions. Using the microsphere method in blood letting dogs, Okada et al. proved that diltiazem elicited the augmentation of both of blood flow and distribution rate in the heart and pancreas, increase in renal, adrenal and large intestinal blood flow without alteration of the distribution rate, and decreases in cerebral and liver blood distribution rate without alteration of the blood flow.15 Further studies of the action of diltiazem on the systemic blood distribution are therefore necessary.

RBF is reported to be not always increased after the administration of diltiazem, but an increase in urinary Na excretion has been described elsewhere.16–18 Funao et al. demonstrated that UV and excretion of electrolyte in the urine are increased in all of patients after the administration of diltiazem except for patients with severe renal disease.16 Tsuichiya et al. reported that although GFR and RBF remained unchanged when renal clearance was measured before and after intravenous injection of diltiazem, \( U_{Na}V \) tended to increase after the drug.18 Based on the fact that the drug exerts an action of increasing \( U_{Na}V \) without causing significant change in renal hemodynamics, Tsuichiya et al. speculated that the site of the action of diltiazem should be the distal tubule of Henle’s ascending limb where the drug actively inhibits sodium transport.18

In the present study it was found that though it was not significant, following the administration of diltiazem the values of GFR and RPF tended to increase gradually as the time proceeded and in contrast \( U_{Na}V \) reached the peak between 1 and 2 hr after the drug indicating statistically significant increase at less than 1% level as compared with \( U_{Na}V \) before the drug. Because percentile renal tubular reabsorption of sodium decreased significantly in agreement with the time of \( U_{Na}V \) peak, it was reasonable to assume that the drug inhibited directly the Na-transport mechanism in the renal tubule. The result of animal experiments by Yamaguchi et al. supports this direct action of the drug14 i.e., because \( U_{Na}V \) was increased by diltiazem even though RBF and GFR were maintained constant by experimental aortic constriction, they pointed out the presence of direct action of the drug on the renal tubule. In addition, they suggested that the site of the

**Fig.1.** Percent increase in \( U_{Na}V \) plotted against percent increase in RPF after diltiazem administration. There was a highly significant correlation between them. Furthermore, an increase in sodium excretion exceeded the corresponding increase in RPF, suggesting that urinary sodium excretion results both from the action through the renal hemodynamics and the direct action on the renal tubule.

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action should be the distal tubule as based on the result of stop-flow study. Abe et al. also indicated that diltiazem has an inhibitory action against the distal renal tubular reabsorption of sodium. However, it is impossible to explain the drug action on sodium excretion by its direct inhibitory action against the tubular reabsorption mechanism alone. In fact, participation of renal hemodynamics in sodium excretion could not be denied by our experimental data, as shown in Fig. 1. For example, when percent increase in RPF after the therapy is compared with that in $U_{Na}V$, the correlation coefficient between them is 0.91, indicating that they are highly correlated each other and that $U_{Na}V$ is situated at above $Y = X$. Hence, an increase in sodium excretion exceeded the corresponding increase in RPF.

This suggests that there are intricate factors which participate in an increase in urinary sodium excretion after the administration of diltiazem and this point cannot be clearly distinguished as to whether an increased urinary sodium excretion results from the action through the renal hemodynamics or the direct action on the renal tubule. According to the theory by Earley et al., the mechanism of action of renal vasodilator drugs is interpreted as follows: The renal perfusion pressure spreads directly to peritubular capillaries resulting in rise of pressure at the site. Active absorption of tissue fluids in the capillaries is disturbed by peripheral Starling’s law, which leads to a decrease in tubular reabsorption. The inhibitory action of the drug through the renal hemodynamics against reabsorption of sodium mainly occurs in the proximal tubule but recent studies have elucidated that sodium reabsorption is also inhibited in the distal tubule.

The practical conclusion is that in human kidney diltiazem exerts a natriuretic action not only through the renal hemodynamics but also by inhibiting directly renal tubular reabsorption of sodium.

REFERENCES


