RENAI HEMODYNAMIC CHANGES ASSOCIATED WITH
ANTIDIURETIC ACTIONS OF CHLORPROPAMIDE,
CLOFIBRATE AND THIAZIDE IN DIABETES INSIPIDUS

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A careful study was performed in two patients of idiopathic diabetes insipidus (DI) to assess the role of renal hemodynamic changes in antidiuresis induced by several agents commonly used for the treatment of DI patients. In one patient, every one of chlorpropamide, clofibrate and thiazide caused a decrease in effective renal plasma flow (ERPF) by about 20% in association with a decrease in urine volume by 40–50%. No significant decrease in GFR was seen in the patient. In the other patient, every one of the above drugs caused a decrease not only in ERPF (by 25–40%) but also in GFR (by 25–35%) in association with a more remarkable decrease in urine volume (by 60–70%). These renal hemodynamic changes resembled those induced by the administration of exogenous vasopressin. Thus renal hemodynamic changes should be taken into consideration when one studies the mechanism of antidiuresis induced by the drugs mentioned above.

Recently several kinds of drugs other than vasopressin have been used for the treatment of polyuria in DI patients. The most commonly used ones are various saluretic drugs and chlorpropamide. Clofibrate was also found to be an effective and relatively safe antidiuretic agent. Despite much investigation, however, the precise mechanism of antidiuresis caused by these agents is still obscure. Since it is well known that renal hemodynamics are closely related to urine concentration process, it seems to be essential at the present time to determine whether or not renal hemodynamic changes are involved in the mechanism of antidiuresis caused by the above drugs.

MATERIALS AND METHODS

Subjects were H.F., a 22 year old man (case 1) and H.H., a 33 year old man (case 2) who were admitted to the hospital complaining of polyuria and polydipsia since several months. Physical examinations and laboratory tests failed to reveal any abnormalities except large volume of dilute urine. Skull X-ray and cerebral angiography disclosed no abnormalities. Carter-Robbins tests and water deprivation tests followed by vasopressin administration were performed and both patients were diagnosed as idiopathic DI.

In order to test the effects of various antidiuretic agents on renal hemodynamics, para-aminohippurate (PAH) clearance and endogenous creatinine clearance were used to estimate ERPF and GFR, respectively. The clearance studies were performed on a carefully controlled protocol. The patients had been provided with diets constant in sodium, total calories and protein content. Water intake was not restricted. On the day of clearance studies the patients were given 500 ml water orally at 9:00 a.m.. At 9:30 a.m. prime injection of PAH was given and an infusion

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Fig. 1. Changes in ERPF observed in association with antidiuresis caused by various agents. Comparing two cases, the changes in ERPF was proportional to the degree of antidiuresis.

Fig. 2. Changes in GFR observed in association with antidiuresis caused by various agents.

of isotonic saline containing PAH was started at a rate of 3 ml/min. Thirty minutes after the prime injection, clearance studies were performed three times for 20 minutes each. The average values obtained from those three clearance periods were used to compare renal hemodynamics in various conditions. The blood samples for PAH and creatinine measurements were taken at the mid-
TABLE I

<table>
<thead>
<tr>
<th>Mo.</th>
<th>Day</th>
<th>Case H. F. ț</th>
<th>Urine Volume ml/day</th>
<th>ERPF ml/min</th>
<th>GFR ml/min</th>
<th>FF</th>
<th>Sp grv</th>
</tr>
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<tbody>
<tr>
<td>4</td>
<td>10</td>
<td>Control (1)</td>
<td>11,000</td>
<td>565</td>
<td>109</td>
<td>0.19</td>
<td>1.002</td>
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<td>466</td>
<td>112</td>
<td>0.24</td>
<td>1.009</td>
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<tr>
<td>4</td>
<td>27</td>
<td>Control (2)</td>
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<td>112</td>
<td>0.21</td>
<td>1.001</td>
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<td>Clofibrate</td>
<td>4,400</td>
<td>464</td>
<td>104</td>
<td>0.22</td>
<td>1.006</td>
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<td>Control (3)</td>
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<td>105</td>
<td>0.18</td>
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<td>5</td>
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<td>Vasopressin</td>
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<td>496</td>
<td>101</td>
<td>0.20</td>
<td>1.016</td>
</tr>
<tr>
<td>5</td>
<td>31</td>
<td>Trichlormethiazide</td>
<td>5,200</td>
<td>463</td>
<td>94</td>
<td>0.20</td>
<td>1.010</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case H. H. ț</th>
<th>Urine Volume ml/day</th>
<th>ERPF ml/min</th>
<th>GFR ml/min</th>
<th>FF</th>
<th>Sp grv</th>
</tr>
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<tbody>
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<td>Control (1)</td>
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<td>620</td>
<td>109</td>
</tr>
<tr>
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<td>10</td>
<td>Control (2)</td>
<td>14,000</td>
<td>626</td>
<td>113</td>
</tr>
<tr>
<td>6</td>
<td>17</td>
<td>Chlorpropamide</td>
<td>4,900</td>
<td>520</td>
<td>79</td>
</tr>
<tr>
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<td>24</td>
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<td>76</td>
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<td>1</td>
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<td>419</td>
<td>79</td>
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<tr>
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<td>397</td>
<td>70</td>
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<tr>
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<td>Control (3)</td>
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<td>712</td>
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<tr>
<td>7</td>
<td>29</td>
<td>Vasopressin</td>
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<td>461</td>
<td>70</td>
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point of each clearance periods. Since water was not administered orally throughout the examination, patients sometimes complained of mild thirst especially when the polyuria was severe.

RESULTS

The effects of oral administration of chlorpropamide (500 mg daily), clofibrate (3000 mg daily) and trichlormethiazide (4 mg daily) on renal hemodynamics were tested when the antidiuretic effects by each of them became apparent and were stabilized.

In case H.F, the antidiuresis by any one of the above drugs was accompanied by a decrease in ERPF (by about 20%) but not by a decrease in GFR. In case H.H, it was accompanied by a decrease in ERPF (by 25-40%) and GFR (by 25-35%). These changes in ERPF and GFR were of similar degree to those induced by exogenous vasopressin (pitressin tannate in oil) of which 2 U was injected intramuscularly in early morning of the day of clearance studies (Table I and Fig. 1 and 2).

As for filtration fraction (FF), no consistent changes were seen in relation to antidiuresis (Table I).

The degree of antidiuresis brought about by the above drugs was remarkable in case H.H when compared to that in case H.F. This may well be related to the fact that the decrease in ERPF induced was much more evident in the former than in the latter (Fig. 1). Also, the decrease in GFR was apparent only in the former case (Fig. 2).

DISCUSSION

Havard and Wood reported that antidiuresis induced by thiazide was associated with a fall in GFR. Although this view has not been generally accepted, there seems to be a close relationship between the antidiuretic effect of saluretic drugs and the creation of body deficit of sodium with a subsequent change of renal hemodynamics.

As for the antidiuretic action of chlorpropamide, on the other hand, the most widely held view is that the drug potentiates the effect of vasopressin to increase water permeability of the distal nephron. In fact, there are several in vivo and in vitro studies which seem to support the view. However, there are also some observa-
tions which cannot be explained by "the increase of water permeability of distal nephron". Firstly, Zweig, Ettinger and Earley observed in dogs undergoing water diuresis that chlorproamide brought about antidiuresis and even anantinatriuresis which were accompanied by a fall in GFR.12 Secondly, two groups found in mammals natriuresis with an associated increase in GFR after chlorproamide injection.6,13

Although these observations seem conflicting each other, this paradoxical behavior of chlorproamide may be meaningful. Several other agents, which are vasoactive, also show similar paradoxical actions on tubular reabsorption of sodium (e.g. angiotensin, norepinephrine, guanethidine, isoproterenol and its derivatives, I-dopa and prostaglandins). Since vasoactive agents influence not only on renal vessels but also on systemic vessels and/or heart muscles, their effects on renal tubular reabsorption are not simply related to their renal actions. They have indirect effects as well which are mediated by systemic hemodynamic changes such as cardiac output and blood pressure and so forth.

Although the effects of chlorproamide on systemic vessels are still not known, it has been recently reported that sulfonyleurea drugs act on heart muscles14 Thus paradoxical actions of chlorproamide may be in some way related to its hemodynamic effects.

As far as the mechanism of chlolfibrate induced antidiuresis is concerned, essentially no information is available at the present time.

Berliner and Davidson demonstrated that if the GFR of one kidney is reduced by partial occlusion of the renal artery, urine osmolality increases in the absence of vasopressin. Also Abbrecht and Malvin suggested that the renal plasma flow (RPF) has an independent effect on urine concentration in addition to its indirect effect on GFR.3 Zweing et al. concluded that the fall in GFR induced by chlorproamide in their study was not of the magnitude previously reported to produce a rise in urine osmolality in the absence of vasopressin12 Although they stated that renal blood flow remained unchanged during the infusion of chlorproamide, they presented no data about it.

In the present study, on the other hand, although a fall in ERPF was seen in the both patients coincident with antidiuresis, no significant change in GFR was seen in case H.F., in whom antidiuretic effects were less remarkable than in case H.H. The fall in ERPF may have caused a decrease in hydrostatic pressure in the peritubular capillaries, although it is also possible that a fall in ERPF out of proportion to a fall in GFR increased the oncotic pressure in peritubular capillaries. (Although FF did not always increase in association with antidiuresis, usual clearance studies may not have been precise enough to detect a small change in FF.)

An increase in capillary uptake of tubular reabsorbate, caused either by a decrease in hydrostatic pressure or by an increase in oncotic pressure in peritubular capillaries, is expected to augment proximal reabsorption15 and thus to decrease the distal delivery of tubular fluid which is necessary for free water formation.

Furthermore, one would have to take into consideration the role of medullary blood flow. Although ERPF mainly represents cortical plasma flow, the decrease in cortical plasma flow may have been accompanied by a decrease in medullary blood flow and a concomitant decrease in removal of solute from the medullary interstitium.16 This in turn may have contributed to production of concentrated urine. An interesting thing is that exogenous vasopressin brought about renal hemodynamic changes similar to those by other antidiuretic agents. This may mean that the effect of vasopressin on urine concentration is related not only to its effect on water permeability of distal nephron but also to some intrarenal hemodynamics, such as intrarenal physical forces and medullary blood flow.

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