The Influence of High and Low Potassium Diet on the Sodium Retaining Effect of Desoxycorticosterone Acetate in Dogs

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Despite various theories on the mechanism of the appearance of DOCA escape, the nature of this phenomenon still remains unknown. In this study the influence of a high or low potassium diet on the sodium retaining effect of DOCA was investigated in dogs.

A low potassium diet facilitated the appearance of DOCA escape, while a high potassium diet delayed its appearance. The rise of blood pH was facilitated by a low potassium diet and inhibited by a high potassium one. Based on these results, the change in blood pH appears to be one of the factors contributing to the development of DOCA escape.

When desoxycorticosterone acetate (DOCA) was administered daily to normal subjects, sodium and water retention occurs for the first 5 to 10 days. After the retention of Na and water, however, Na excretion increased and the balance of Na was maintained despite continued administration of DOCA. This phenomenon was called DOCA escape by Relman et al.\textsuperscript{1} Despite various theories on the mechanism of the appearance of DOCA escape,\textsuperscript{2–7} the nature of this phenomenon still remains unknown.

In primary aldosteronism, administration of DOCA scarcely causes Na retention. On the other hand, serum potassium level is usually low and metabolic alkalosis is present in this disease. In view of these facts, the author thought that hypokalemia and alkalosis may participate in the mechanism of DOCA escape. In this study the influence of hypokalemia on the appearance of DOCA escape was investigated in dogs. Hypokalemia was induced by a low K diet and administration of hydrochlorothiazide. The influence of hyperkalemia induced by high K diet and KCl administration upon the DOCA escape was also investigated.

METHODS

Adult female dogs weighing 9.3–16 kg, perineotomized beforehand and kept individually in a cage with steel net bottom for the convenience of urine sampling, were used for the experiment.

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1) Preliminary experiment

As a preliminary experiment, the mode of appearance of DOCA escape was studied with dogs given a rather large amount of Na. Four dogs were divided into 2 groups of 2 dogs each. Both groups were given 85–105 mEq of Na a day, while 40–50 mEq of K were given to the first group and 15–20 mEq of K were given to the second group.

The first 10–15 days of the experiment were the control period in both groups. After establishment of the Na balance during this period, 20 mg of DOCA were intramuscularly injected every day. DOCA escape was found to occur on the first or second day. It might be concluded that DOCA escape occurred one or two days after the start of DOCA administration regardless of K intake when Na intake was abundant. K intake does not appear to have significant influence upon the appearance of the escape.

Na intake should therefore be kept low in order to study the effect of K intake on DOCA escape. Na intake was thus restricted to 5–7 mEq/day in the following main experiments.

2) Main experiments

Six dogs were divided into three groups; the control (Nos. 1 and 2), high K intake (Nos. 3 and 4) and low K intake groups (Nos. 5 and 6). Table 1 shows the composition of the diet given to each dog. Boiled rice constituted the main part, while whale meat was added in high K group and cow's milk in low K group. In addition, 5.1–6.8 mEq/day of NaCl were given daily and 13.3 mEq/day of KCl in high K group. In each animal, body weight, water intake, urinary volume, and excretion of Na and K in urine were determined daily. Hematocrit, serum protein, serum Na, and blood pH were measured at a few days' intervals. A Hitachi flame photometer was used for the determination of Na and K, and a Hitachi pH-meter with glass electrodes (Model P) was used for blood pH determination. For the determination of Na and K in stool, stool samples were collected separately during the control period and during DOCA administration. Stool was heated and ashed with addition of nitric acid, and was diluted to an adequate concentration for the determination of Na and K.

In each group, a 17–42 day period before the administration of DOCA or hydrochlorothiazide was taken for control observation and the results obtained during this period were compared with those during DOCA administration. The length of the control period in each animal and the average urinary excretion of Na and K are shown in Table 2. Na

| Table 1. Diet of experimental dogs (average intake per day) |
|-------------|-------------|-------------|-------------|-------------|-------------|
| Dog No.    | Rice g      | Whale meat g| Milk ml     | NaCl g (Na mEq) | KCl g (K mEq) |
|            |             |             |             | (6, 8)        | (13,3)       |
| Control dogs | 1           | 100         | 70          | 0.4           | 2.0          |
|             | 2           | 100         | 35          | 0.35          | 0.3          |
|            |             |             |             | (5.95)        | (5.1)        |
| Dogs on high potassium diet | 3           | 200         | 100         | 0.4           | 0.3          |
|             | 4           | 250         | 100         | (6, 8)        | (13,3)       |
|            |             |             |             | (5.1)        | (2.0)        |
| Dogs on low potassium diet | 5           | 100         | 300         | 0.4           | 0.4          |
|             | 6           | 100         | 300         | (6, 8)        | (6, 8)       |

Na and K content in 100 g of rice: Na = 0, K = 2.7–3.3 mEq.
Na and K content in 100 g of whale meat: Na 0.1 mEq, K = 6.4–6.9 mEq.
Na and K content in 100 ml of milk (treated with Amberlite MD-3): Na = 0.2 mEq, K = 0.
Low K Diet and DOCA Escape

TABLE 2. Average excretion of Na and K in urine per day during control period in dogs on a normal diet and in those on high and low potassium diet

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Control period (days)</th>
<th>Excretion in urine per day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Na (mEq)</td>
</tr>
<tr>
<td>Control dogs</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>Dogs on high potassium diet</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>Dogs on low potassium diet</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>28</td>
</tr>
</tbody>
</table>

excretion was not very different among three groups. K excretion was 7.85 and 5.57 mEq/day in the control group, while the high K group excreted K in 25.4 and 27.61 mEq/day and the low K group excreted K in only 2.74 and 2.54 mEq/day.

In control and high K groups daily intramuscular injection of 20 mg of DOCA was started immediately after the end of the control period. In Nos. 5 and 6 of low K group, serum K fell to 3.20 and 3.30 mEq/l, respectively. As this indicated that low K diet alone could not induce a state of marked hypokalemia, 25 mg of hydrochlorothiazide was administered in combination with low K diet for 26 days. Serum K decreased to 2.55 mEq/l, in No. 5 through this procedure. Upon discontinuation of hydrochlorothiazide, serum K again rose gradually, but stayed as low as 3.00 mEq/l at the start of DOCA administration on the 15th day.

In No. 6 on low K diet, similar administration of hydrochlorothiazide for 26 days lowered the serum K to 2.62 mEq/l. Although some elevation was seen after the discontinuation of the administration, the level was 3.00 mEq/l at the start of DOCA administration on the 4th day. Following results were obtained when DOCA was administered in 3 groups of 6 dogs after such pretreatment.

RESULTS

1) Normal control group (Nos. 1 and 2)

Na retention occurred upon DOCA administration and was followed by the escape on the 21st day in No. 1 (Fig. 1) and on the 15th day in No. 2 (Fig. 2). Meanwhile, the body weight increased by 640 g in No. 1 and 280 g in No. 2. Serum Na was unchanged in both Nos. 1 and 2, while serum K definitely decreased from 3.88 to 2.66 mEq/l in No. 1 and from 3.70 to 2.72 mEq/l in No. 2. Blood pH rose distinctly from 7.39 to 7.42 in No. 1 and from 7.39 to 7.43 in No. 2.

2) High K group (Nos. 3 and 4)

The serum K value during the control period in this group (Figs. 3 and 4) was 4.30–4.12 mEq/l being slightly higher than those in the normal control group (3.88 to 3.70 mEq/l). However, serum Na did not show a great difference. Upon DOCA administration, Na retention was seen also in this group. The appearance of escape was on the 29th day in No. 3 and 31st day in No. 4, showing a delay as compared with that in normal controls. The body weight increased by
Fig. 1. Effects of DOCA on Na balance, blood pH, serum Na and K concentration and body weight in a control dog (dog 1). E: appearance of escape.

Fig. 2. Effects of DOCA on Na balance, blood pH, serum Na and K concentration and body weight in a control dog (dog 2). E: appearance of escape.

700 g in No. 3 and 600 g in No. 4 during this period. Serum Na was unchanged both in Nos. 3 and 4, as compared with values before DOCA administration, while serum K decreased from 4.30 to 3.75 mEq/l and from 4.12 to 4.00 mEq/l through DOCA administration, without marked changes. Blood pH slightly rose from 7.37 to 7.39 in No. 3 and from 7.35 to 7.39 in No. 4, the change being not remarkable.

3) Low K group (Nos. 5 and 6)

As stated before, feeding on low K diet alone did not cause a marked hypo-
kalemia in this group. Administration of hydrochlorothiazide, 25 mg a day, caused hypokalemia, K values ranging from 2.55 to 2.62 mEq/l. When Na balance changed from positive to negative (3-15 days), administration of DOCA was started. The escape occurred on the 10th day in No. 5 (Fig. 5), and on the 12th day in No. 6 (Fig. 6). Body weight increased by 260 g in No. 5 and 300 g in No. 6 during this period. Serum Na was unchanged in both animals, while serum K distinctly decreased from 3.00 to 2.32 mEq/l in No. 5, and from 3.00 to 2.48 mEq/l in No. 6. Along with these changes blood pH definitely rose from 7.40 to 7.45 in No. 5 and from 7.39 to 7.38 in No. 6.
Fig. 5. Effects of DOCA on Na balance, blood pH, serum Na and K concentration and body weight in a dog on a low potassium diet (dog 5). E: appearance of escape.

Fig. 6. Effects of DOCA on Na balance, blood pH, serum Na and K concentration and body weight in a dog on a low potassium diet (dog 6). E: appearance of escape.
Low K Diet and DOCA Escape

DISCUSSION

Concerning the mechanism of DOCA escape, elevation rate of GFR or increase in extracellular fluid volume has been regarded as responsible for its development. However, de Wardener et al. 5 (1) administered a large amount of mineralocorticoid and (2) experimentally decreased GFR through constriction of the thoracic aorta, but failed to prevent the increase in Na excretion upon infusion of sodium chloride. They thus demonstrated that the main cause of increased Na excretion was neither the decrease in aldosterone secretion nor the elevation of GFR, but a third factor or the decrease of Na reabsorption by renal tubules must be taken into consideration. As the result of administration of aldosterone in normal subjects, Rovner et al. 7 pointed out the importance of a humoral factor inhibiting renal tubular Na reabsorption based on their observations of the absence of changes in blood pressure, GFR, volume of extracellular fluid and serum Na concentration before and after the development of the escape. Gill et al., 6 on the other hand, facilitated DOCA escape through administration of guanethidine and obtained a result suggesting the participation of a neural factor.

Concerning the influence of Na intake upon DOCA escape, rapid development of escape by Na loading and delayed development by Na restriction have been pointed out.2-4 When Na is not restricted in dogs, DOCA escape is known to occur on the first or second day.3 The present author has also confirmed this phenomenon. However, DOCA escape did not take place in the experiments of Na restriction in dogs until the 15th to the 20th day. The author has therefore investigated the influence of K intake under Na restriction and found the rapid appearance of escape phenomenon in the group maintained in low K diet, and a delayed appearance in the group of high K diet.

Administration of DOCA generally causes alkalosis. In normal subjects blood pH is influenced by Na or K intake.8-12 14 On the contrary, it does not readily rise upon Na restriction but it promptly rises upon K restriction when DOCA is given. Roth and Gamble13 pointed out a rapid occurrence of alkalosis in dogs upon DOCA administration when the animals were maintained on high Na and low K diet, and a slow occurrence in cases of low Na and high K diet. The author changed K intake to two levels of high and low under a common condition of Na restriction. Blood pH was found to elevate more markedly in low K diet group than in high K diet one, as in the study of Roth and Gamble. The escape appeared rapidly in low K diet group and slowly in high K diet one. This might indicate that the escape phenomenon occurred rapidly when the rise of blood pH was facilitated, but slowly when it was delayed, suggesting an intimate relationship between blood pH and the time of the appearance of the escape phenomenon.

As to the mechanism of the action of some hormones, it has been suggested that they manifest their effects through activation of enzymes. It is quite conceivable that enzyme activity is influenced by the change of blood pH. From this point of view, the results of the present study may suggest that the change in
blood pH is one of the factors producing DOCA escape.

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References


