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# THE INFLUENCE OF SODIUM AND POTASSIUM SUPPLEMENTS ON THE DIURETIC RESPONSES TO FRUSEMIDE ADMINISTRATION IN NORMAL SUBJECTS

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**1** Twelve normal subjects received (1) normal diet, (2) normal diet with 100 mmol supplementary sodium chloride and (3) normal diet with 96 mmol supplementary potassium chloride, each for 10 days, in a balanced cross-over study according to a Latin Square design. At the end of each study period, the subjects received 80 mg frusemide orally. Each study period was separated from the other by 10 days.

**2** Changes in urinary electrolyte excretion occurred within the first four days of each dietary period then remained constant, with significant differences in urinary Na/K ratio between the dietary regimes.

**3** Between-subject correlations, using the mean values over the three study periods, demonstrated significant associations between plasma uric acid and urinary Na/K ratio and between plasma prolactin and urinary potassium excretion.

**4** Urinary potassium excretion and Na/K ratio following frusemide were influenced significantly by alteration of diet but there was no change in sodium excretion.

**5** Between-subject correlations of pretreatment variables with diuretic response, using the mean values over the three study periods, demonstrated significant associations between both pretreatment urinary Na/K ratio and plasma uric acid and respectively the urinary potassium excretion and urinary Na/K ratio in response to frusemide.

**6** While the response to frusemide was altered by short-term changes in dietary sodium and potassium, the difference was less than expected from observations in two populations with customary diets differing in similar manner.

## Introduction

There is wide inter-subject variation in response to diuretics, even among normal individuals. Part of the variation in diuretic response to the loop diuretics, frusemide and bumetanide and to the aldosterone antagonists, spironolactone and prorenoate potassium, has been related to variations in several pretreatment parameters, namely urinary Na/K ratio, plasma uric acid, plasma prolactin and urinary aldosterone excretion (Ramsay, Auty, Horth, Levine, Shelton & Branch, 1975; Ramsay, Hessian & Tidd, 1975; Levine, Ramsay, Auty, Branch & Tidd, 1976; Branch, Read, Levine, Vander Elst, Shelton, Rupp & Ramsay, 1976). Since both urinary Na/K ratio and urinary aldosterone excretion are influenced by dietary intake of sodium and potassium, diet may modify the apparent diuretic response. This concept was supported in a study in which the same protocol was used to compare the responses to frusemide and bumetanide in normal subjects in England and Germany. Significant differences in response to the drugs between subjects from the two countries were related to differences in dietary intake of sodium and potassium (Branch *et al.*, 1976).

The present study was designed to evaluate the hypothesis that changes in dietary intake of sodium and potassium would influence the response to a standard dose of frusemide in healthy subjects.

## Methods

Twelve healthy male volunteers aged 20 to 24 years gave informed consent to participate in the study, which was approved by a hospital ethics committee. The study consisted of three 11-day treatment periods, each separated by 10 days. Each of the six possible treatment sequences was administered to 2 subjects according to a Latin Square design. Treatments were: (1) normal diet, no specific treatment; (2) normal diet plus sodium chloride 100 mmol per day, for 10 days (10 Slow Sodium (Ciba) tablets in divided doses); (3) normal diet plus potassium chloride 96 mmol per day for 10 days (12 Slow K (Ciba) tablets in divided doses).

Urine collections were made each 24 h throughout the treatment periods from 09 h 00 min to 09 h 00 min the following morning. At 09 h 00 min on the eleventh day, 80 mg frusemide (Hoechst) was administered orally and urine was collected over the subsequent 8 h. Blood samples for uric acid were collected at 09 h 00 min on days 2, 4, 6, 9, 10 and 11 in each trial period. Plasma samples for prolactin estimation were collected at 09 h 00 min, 13 h 00 min and 18 h 00 min on day 10. Consumption of alcohol was limited. Ingestion of any medication or liquorice was not allowed. Personal salt dispensers were issued to all subjects to be used where salt was added at the table. These were weighed at the beginning and end of each trial period so that an estimate of differences in appetite for salt could be made. Urine sodium and potassium concentrations were measured by means of a flame photometer with lithium internal standardization. Urinary aldosterone excretion on day 10 of each treatment was measured by a radioimmunoassay method previously described by Branch *et al.* (1976). Plasma uric acid was measured by a modification of the automated phosphotungstate colorimetric method (Nishi, 1967). Plasma prolactin was measured by radioimmunoassay (Cole & Boyns, 1973).

## Results

There was no significant difference in the amount of salt added at table during the different treatments. On sodium treatment, the urinary Na/K ratio rose over the first three days to achieve a stable level between days 4 to 10 (Figure 1). Similarly, during potassium supplementation and on a normal diet the urinary Na/K ratio remained constant between days 4 to 10 (Figure 1). There was no significant change in 24 h urinary creatinine excretion over the 10 days of each study period (Figure 1). Due to considerable day to day variation in urinary excretion of sodium and potassium in individual subjects, the mean values

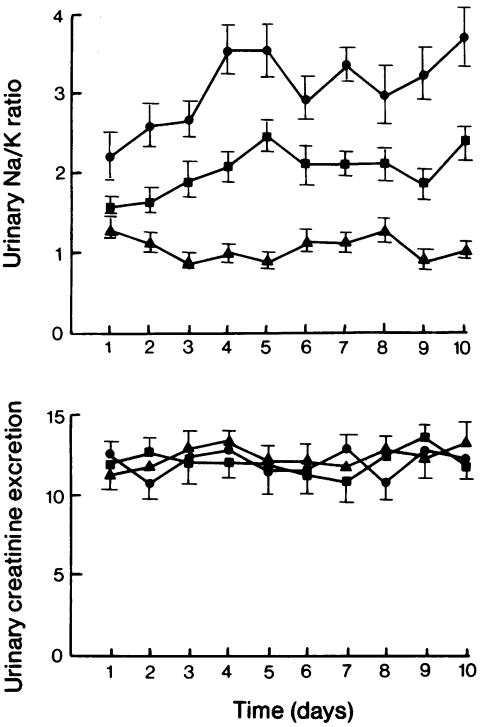


**Figure 1** Urinary Na/K ratio and 24 h urine creatinine excretion in 12 normal subjects who received 100 mmol Na (●), 96 mmol K (▲) or no supplements (■) for ten days in a Latin Square design study. Differences between study periods for urinary Na/K ratio are significantly different ($P < 0.05$) from days 2 to 10. There were no significant differences between periods in creatinine excretion.

between days 4 and 10 in each subject were calculated (Table 1). Sodium loading caused a significant increase in sodium excretion and potassium loading significantly increased potassium excretion. In neither case was the increase as large as the supplementary oral intake nor was there a change in the urinary excretion of the other anion. Aldosterone excretion was significantly increased after 10 days on supplemental potassium but was not significantly influenced by increased sodium intake. Plasma uric acid and plasma prolactin did not change significantly with different dietary regimens.

On the 11th day of each period, frusemide induced a brisk diuresis which was complete within 8 h. The urinary electrolyte pattern following frusemide was significantly influenced by the preceding dietary regimen. Potassium excretion was higher and the urinary Na/K ratio lower following potassium treatment and *vice versa* following sodium treatment. There was

**Table 1** Comparison of parameters in 12 normal male volunteers after receiving 100 mmol sodium, 96 mmol potassium or no added supplements for a period of 10 days in a Latin Square design study

| *Response variable* | *Sodium loading* | *Control* | *Potassium loading** | *Statistical significance of difference* | *Pair comparisons* |
|---|---|---|---|---|---|
| 24 h urine sodium (mmol/24 h) | 141.8 | 91.3 | 87.0 | $P < 0.001$ | Sodium loading > other two ($P < 0.01$), control and K loading NS |
| 24 h urine potassium (mmol/24 h) | 45.8 | 43.6 | 91.9 | $P < 0.001$ | K loading > other two ($P < 0.01$), control and Na loading NS |
| Sodium/potassium ratio | 3.34 | 2.16 | 1.01 | $P < 0.001$ | All three differ from each ($P < 0.01$) |
| Aldosterone excretion (nmol/24 h) | 1.13 | 1.21 | 2.51 | $P < 0.005$ | Potassium loading > other two ($P < 0.01$), control and sodium loading NS |
| Plasma uric acid (mmol/l) | 0.352 | 0.367 | 0.369 | NS | |
| Plasma prolactin (mu/ml) | 0.165 | 0.124 | 0.116 | NS | |

Sodium and potassium excretion are mean values from each subject of serial 24 h urine samples from day 4 to day 10. Plasma uric acid are mean values from days 4, 6, 9 and 10. Plasma prolactin are mean values of samples drawn at 08 h 00 min, 12 h 00 min and 18 h 00 min on day 10. Means of each treatment have been compared by analysis of variance and the Newman Keuls multiple comparison technique.

* Mean for potassium loading includes two estimated missing values in the 12 observations averaged.

NS: not statistically significant, $P > 0.05$.

a trend for sodium excretion to be higher in subjects receiving sodium treatment and lower during potassium treatment but this was not significant (Table 2).

The Latin Square study design allowed a comparison of parameters with respect to time and this demonstrated significant differences in the mean results for different study periods (Table 3). These differences with time do not bias the comparisons between the three dietary regimens presented above, since the study was designed specifically to deal with

**Table 2** Comparison of 8 h diuretic response to 80 mg frusemide when administered orally to 12 normal male volunteers who had received 100 mmol sodium, 96 mmol potassium or no added supplements for 10 days in a Latin Square design study

| *Response variable* | *Sodium loading* | *Control* | *Potassium loading* | *Statistical significance of difference* | *Pair comparisons* |
|---|---|---|---|---|---|
| Urinary sodium excretion (mmol) | 141.4 | 134.4 | 121.6 | NS | |
| Urinary potassium excretion (mmol) | 28.8 | 35.8 | 42.0 | $P < 0.001$ | All three differ from each other, control v potassium loading ($P < 0.05$) otherwise ($P < 0.01$) |
| Urinary sodium/potassium ratio | 5.28 | 3.78 | 2.98 | $P < 0.001$ | All three differ from each other, control v potassium loading ($P < 0.05$) otherwise ($P < 0.01$) |

Means of each treatment have been compared by analysis of variance and the Newman Keuls multiple comparison technique.

**Table 3** Comparison of parameters obtained in 12 normal male volunteers in the three study periods in the sequence that subjects were tested in the Latin Square design

| *Response variable* | *Treatment period 1* | *Treatment period 2* | *Treatment period 3* | *Statistical significance of difference between means* |
|---|---|---|---|---|
| 24 h urine sodium (mmol/24 h) | 106 | 102 | 113 | NS |
| 24 h urine potassium (mmol/24 h) | 68 | 54 | 59 | $P < 0.025$ |
| Sodium/potassium ratio | 1.87 | 2.20 | 2.44 | $P < 0.05$ |
| Plasma uric acid (mmol/l) | 0.35 | 0.38 | 0.36 | $P < 0.05$ |
| Plasma prolactin (mu/ml) | 0.092 | 0.100 | 0.213 | $P < 0.001$ |

Sodium and potassium excretion are mean values from each subject of serial 24 h urine samples from day 4 to day 10. Plasma uric acid are mean values from days 4, 5, 9 and 10. Plasma prolactin are mean values of samples drawn at 08 h 00 min, 12 h 00 min and 18 h 00 min on day 10. Means of each of the study periods have been compared by analysis of variance.
NS: not statistically significant, $P > 0.05$.

this eventuality. However, the trend to change with time would be expected to weaken seriously correlations between variables *within* any dietary regime. For this reason the mean of the results during the three dietary periods was calculated for each subject in order to investigate possible inter-subject relationships between urine electrolyte excretion, plasma uric acid and plasma prolactin. When these parameters were compared during the period of dietary supplementation, there was a significant negative correlation between plasma uric acid and urinary Na/K ratio (Table 4, Figure 2).

The mean plasma prolactin did not correlate with either sodium or potassium excretion. Plasma prolactin measured during the placebo period alone, however, showed a significant positive correlation with the mean potassium excretion of all three treatment periods and there was a trend towards a positive relationship with sodium excretion (Figure 3).

A similar analysis of inter-subject relationships between pre-frusemide variables and the diuretic response demonstrated significant correlations of the urinary Na/K ratio before frusemide with urinary potassium excretion and the urinary Na/K ratio in response to frusemide (Table 5, Figure 4). Furthermore, pretreatment mean plasma uric acid levels showed a significant negative correlation with the urinary Na/K ratio after frusemide (Figure 2).

## Discussion

This study has confirmed the original hypothesis that changes in the dietary intake of sodium and potassium can influence the urinary electrolyte excretion in response to the loop diuretic, frusemide. However, the differences in response to frusemide between the three treatments (Table 2) were smaller than antici-

**Table 4** Product-moment correlation coefficients between mean observations over three study periods in 12 normal subjects

| | *Aldosterone excretion* | *Plasma prolactin* | *Plasma prolactin (placebo only)* | *Sodium excretion* | *Potassium excretion* | *Na/K ratio* |
|---|---|---|---|---|---|---|
| Plasma uric acid | +0.52 | −0.36 | −0.23 | −0.48 | −0.12 | −0.62* |
| Aldosterone excretion | | +0.13 | −0.37 | −0.32 | −0.31 | −0.41 |
| Plasma prolactin | | | | +0.52 | +0.19 | +0.15 |
| Plasma prolactin (placebo only) | | +0.15 | | +0.47 | +0.65* | −0.20 |

* $P < 0.05$.

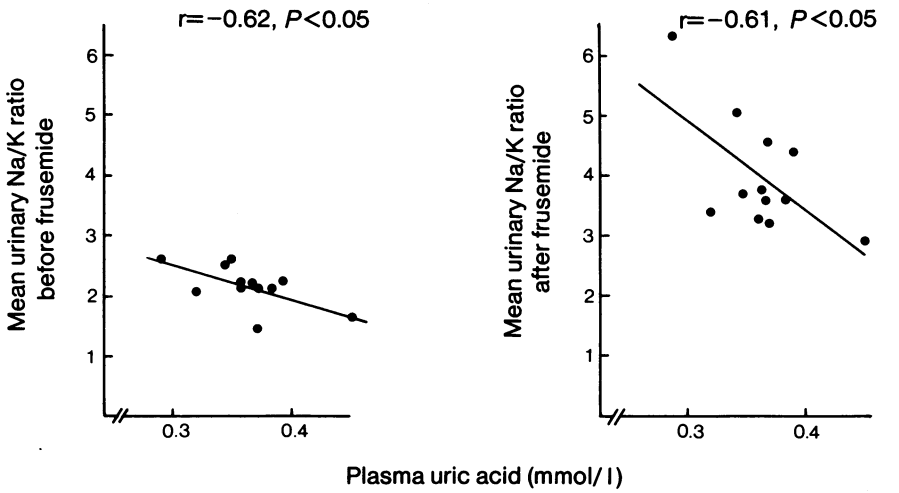


**Figure 2** The relationship between the mean plasma uric acid observations over the three study periods and the urinary Na/K ratio before and after the administration of frusemide in 12 normal subjects.

pated. It was previously observed that a group of normal German subjects who had a greater sodium and a smaller potassium dietary intake than a comparative group of normal English subjects, had a 30% greater urinary sodium excretion and 20% smaller urinary potassium excretion in response to similar doses of frusemide and bumetanide (Branch *et al.*, 1976). In that study, differences between subjects and between populations in urinary sodium, potassium and Na/K ratio following frusemide could be explained by differences in the pretreatment urinary Na/K ratio. However, it was not possible to decide whether changes in sodium intake, potassium intake or their indirect influence on renal control mechanisms were responsible for the differences in diuretic response. In the present study, even though the anticipated trend was present, the failure to induce a significant change in urinary sodium excretion suggests that a change in diet for 10 days provides less of a stimulus for modifying diuretic response than does a life-long

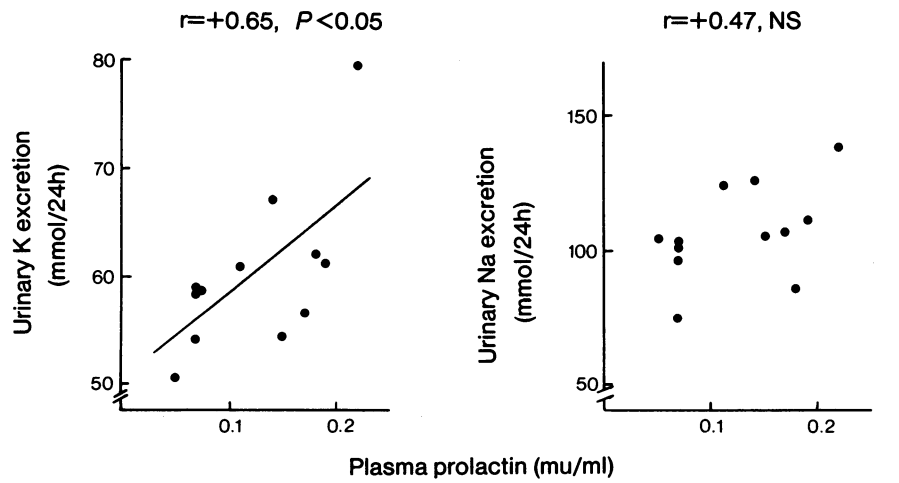


**Figure 3** The relationship between the plasma prolactin concentration obtained in the placebo period and the mean of the three concentrations of the urinary potassium and sodium excretion between days 4 to 10 of each study period.

**Table 5** Product-moment correlation coefficients between mean observations over three study periods in 12 normal subjects relating pre-frusemide variables with the diuretic response

| | *Post-frusemide variable* | | |
|---|---|---|---|
| *Pre-frusemide variable* | *Sodium excretion* | *Potassium excretion* | *Na/K ratio* |
| Urinary Na/K ratio | −0.11 | −0.57* | +0.67* |
| Aldosterone excretion | +0.51 | +0.27 | +0.03 |
| Plasma uric acid | +0.06 | +0.65* | −0.61* |
| Plasma prolactin | +0.55 | +0.23 | +0.21 |
| Plasma prolactin (placebo only) | −0.30 | +0.02 | −0.42 |

* $P < 0.05$.

dietary intake. This implies that diuretic responsiveness may be determined by control mechanisms which take a long period of time to adjust and which may possibly be related to factors regulating electrolyte appetite.

In spite of the relatively small changes in response between treatments, the pretreatment urinary Na/K ratio related significantly to urinary potassium excretion and urinary Na/K ratio after frusemide (Table 5, Figure 4). This relationship has now been observed between populations (Branch *et al.*, 1976), in normal subjects on different dietary intakes of sodium and potassium and in patients with congestive heart failure and cirrhosis (Alexander, Levine, Branch & Hartog, 1977). The urinary Na/K ratio has been thought to be largely determined by aldosterone activity. However, in the present study direct measurements of aldosterone excretion did not correlate with the urinary Na/K ratio. This suggests that the latter parameter is the end result of a complex interaction of more than one controlling mechanism. Irrespective of the underlying control, the urinary Na/K ratio provides a simple method for anticipating the extent of diuretic response in subjects with a normal glomerular filtration rate and is particularly useful in allowing prediction of those patients who require potassium replacement therapy (Alexander *et al.*, 1977).

The observed relationship between plasma uric acid and electrolyte excretion before and after a diuretic drug (Figure 2, Tables 4 and 5) is consistent with previous observations with frusemide (Ramsay *et al.*, 1975; Branch *et al.*, 1976). It is unlikely that there is a direct relationship between uric acid and frusemide as similar relationships between plasma uric acid and the urinary Na/K ratio have been observed following spironolactone therapy alone (Ramsay, Shelton & Harrison, 1977), fludrocortisone treated normal subjects receiving spironolactone or pro-

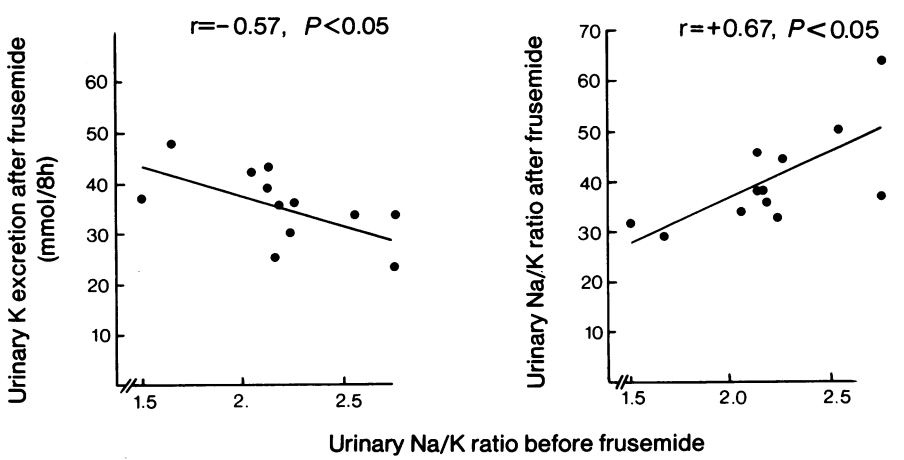


**Figure 4** The relationship between the mean prefrusemide observations of the urinary Na/K ratio over the three study periods and the mean urinary potassium excretion and urinary Na/K ratio following frusemide.

renoate potassium (Ramsay *et al.*, 1975) and sodium depleted subjects receiving spironolactone (Levine *et al.*, 1976). These observations suggest a general relationship between plasma uric acid and diuretic response. It is possible that uric acid production in normal subjects is a function of lean body mass, in a similar fashion to creatinine production, and that variations between subjects in plasma uric acid concentration reflects variations in renal uric acid clearance. Thus, the relationship between plasma uric acid concentration and diuretic response may be due to common factors that control renal tubule function. Renal tubular reabsorption and secretion of uric acid are generally considered to occur in the proximal tubule (Steele, 1969), while fine sodium modulation and potassium secretion occur in the distal tubule (Gross, Imai & Kokko, 1975), ascending limb of Henle (Rocha & Kokko, 1973) and collecting duct (Grantham, Burg & Orloff, 1970). A further understanding of possible controlling factors for both functions would increase our understanding of renal tubular control mechanisms.

Based on the observation that administration of ovine prolactin to man induces urinary sodium and potassium retention, it has been suggested that this hormone is of importance as a control mechanism for renal tubule function (Horrobin, Lloyd, Lipton, Burstyn, Durkin & Muiruri, 1971). Significant relationships have previously been observed between endogenous plasma prolactin concentration and urinary sodium excretion following frusemide administration (Auty, Branch, Cole, Levine & Ramsay, 1976). However, in that study neither changes in dietary intake of sodium and potassium nor acute sodium deprivation were able to influence plasma prolactin concentration (Auty *et al.*, 1976). Similarly, in the present study neither sodium nor potassium supplements to the diet influenced plasma prolactin, however, the plasma prolactin concentration of the placebo period did have a significant positive relationship with potassium excretion during the period before frusemide administration (Figure 3) but not to the diuretic response. Whether this is due to a direct cause and effect relationship between endogenous prolactin and renal function still remains to be determined, but an indirect relationship seems equally probable.

In conclusion, this study has demonstrated that the urinary electrolyte excretion response to frusemide can be influenced by both sodium and potassium supplements to the diet of normal subjects. Furthermore, the electrolyte excretion after frusemide is related to pretreatment factors controlling renal homeostasis before drug administration.

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