Serum Magnesium Level in the Salt-losing Type of Congenital Adrenal Hyperplasia

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Evidence has accumulated that aldosterone plays an important part in the regulation of magnesium metabolism in experimental animals. There is, however, little information concerning the effect of aldosterone on the metabolism of magnesium in man. Mader and Iseri (1955) and Milne, Muehrcke, and Aird (1957) reported a single case of primary aldosteronism, with tetany and paralysis, in which low serum levels of magnesium and potassium were observed. Harrop et al. (1933) and Zwemer and Sullivan (1934) described high serum levels of magnesium in animals with adrenal insufficiency. Investigations have been made into the effects of mineralocorticoids upon the metabolism of magnesium and other electrolytes using adrenalectomized animals (Conway and Hingerty, 1946; Hingerty, 1957; DaVanzo, Crossfield, and Swingle, 1958; Weil and State, 1958). It has been generally agreed that serum potassium and magnesium are conspicuously raised, with parallelism in mineralocorticoid deficiency, and that mineralocorticoids increase the renal excretion of magnesium as well as of potassium.

In the salt-losing type of congenital adrenal hyperplasia (CAH) which is commonly characterized by the defect of 21-hydroxylation in the biosynthesis of cortisol and aldosterone in the adrenal cortex, it is assumed that serum potassium and magnesium levels are raised. However, there have been no reports on magnesium metabolism in CAH. Accordingly, this investigation reports the serum magnesium level and its relation to other electrolytes in two infants with the salt-losing type of CAH, who were treated with mineralo- and glucocorticoids plus salt supplement.

**Case Reports**

Two infants with the salt-losing type of CAH, who were 15 days and 5½ months old at the start of the investigation, were studied for 10 days and 7 months, respectively.

**Case 1.** An 11-day-old female infant, born after a normal pregnancy and delivery with a birthweight of 2900 g. and a non-contributory family history, was admitted because of abnormal genitalia and poor weight gain. Physical examination revealed mild dehydration and a common urogenital sinus, with enlarged clitoris. Her weight was 2700 g. and her length 50-0 cm. Hb 19·0 g./100 ml.; white blood cells 17,800/c.mm., with normal differential count. Urinalysis revealed no abnormalities. Serum Na, K, Cl, and CO₂ content were 120, 6·4, 94, and 12·0 mEq/l., respectively. Total protein, total cholesterol, urea N, and GOT in the serum, normal. A buccal smear for sex chromatin was positive. Urinary excretions of 17-ketogenic steroids (17-KGS) measured by a modification of the method of Few (1961), 17-steroids (17-KS) by a modification of the method of Drekter et al. (1952), and pregnanetriol by the method of Bongiovanni and Eberlein (1958) were as follows (figures in parentheses indicate values after the cortisol treatment): 11-deoxy-17-KGS 3·75 mg./24 hr. (1·3); 11-oxo-17-KGS 2·94 mg./24 hr. (1·54); 11-deoxy-11-oxo-17-KGS ratio 1·21 (0·85); 17-KS 1·03 mg./24 hr. (0·94); and pregnanetriol 1·41 mg./24 hr. (0·53). The clinical course is shown in Fig. 1.

**Case 2.** A 1-month-old male infant, born after a normal pregnancy and delivery with a birthweight of 3700 g., was admitted with complaints of poor drinking and prolonged jaundice. His mother had one previous pregnancy resulting in a full-term infant, who died suddenly on the 7th day of life. On admission, physical examination revealed a slightly jaundiced, pigmented, and malnourished infant with body weight of 3090 g. and body length of 54·0 cm. External genitalia were slightly pigmented and both testes were already descended, but no penile hypertrophy was observed. Hb 18·5 g./100 ml.; white blood cells 16,150/c.mm., with normal differential count. Urinalysis revealed slight proteinuria (10 mg./100 ml.). Serum Na, K, Cl, and CO₂ content were 124, 8·7, 92, and 15·8 mEq/l., respectively. Total protein and total cholesterol in the
Case 1
Sodium chloride (g/day orally)

Cortisol (10mg/day orally)

DOC-Trimethylacetate

(20mg, i.m.)

135
120
105
90
75
60
45
30
15
0

Fig. 1.—Clinical course of Case 1.

serum were normal. Urinary excretions of 17-KGS, 17-KS, and pregnanetriol measured by the same methods as in Case 1, and 17-hydroxycorticosteroids (17-OHCS) measured by the method of Glenn and Nelson (1953) were as follows (figures in parentheses indicate values after the treatment with cortisone and cortisol): 11-deoxy-17-KGS 5-30 mg./24 hr. (0-23); 11-oxy-17-KGS 3-65 mg./24 hr. (0-51); 11-deoxy- to 11-oxy-17-KGS ratio 1-45 (0-45); 17-KS 1-29 mg./24 hr. (0-17); pregnanetriol 4-88 mg./24 hr. (0-02); and 17-OHCS 0-7 mg./24 hr. (0-2). The patient was discharged with incomplete recovery, and was followed at the outpatient clinic (Fig. 2).

Serial determinations of urinary steroids showed that the high excretions of 11-deoxy- and 11-oxy-17-KGS, 17-KS, and pregnanetriol were suppressed by the administration of the cortisol therapy in both cases, resulting in a lowering of the 11-deoxy- to 11-oxy-17-KGS ratio. The diagnosis of the salt-losing type of CAH (21-hydroxylase deficiency) was therefore established.

Methods

Five serial blood samples were obtained by venous puncture from Case 1, and 16 samples from Case 2, in order to determine serum concentrations of electrolytes. Serum Na and K were determined by a flame photometric method and serum Cl by the method of Schales and Schales (1941). Serum magnesium concentrations were determined by a modification of the method of Schachter (1961) with Multiplier Fluorescence Meter Model 540 (Photovolt Corporation) using B Hg-1 Filter (wave length, 365 mμ) for the primary filter, and B 520 Filter (wave band, 480-580 mμ) for the secondary one. The fluorometric technique used in this study has been described elsewhere (Kobayashi and Shiraki, 1967). Mean recovery by this method was 96-8%, with a range of 96-2 to 98-0%.

For 16 healthy newborns from 11 to 30 days of age, the mean values of the serum magnesium were 1-68 mEq/l. (SD 0-16), with a range of 1-42 to 1-96 mEq/l., and for 24 healthy infants from 2 months to 1 year, mean values were 2-26 mEq/l. (SD 0-15), with a range of 1-95 to 2-52 mEq/l. (Kobayashi, 1967).

TABLE

<table>
<thead>
<tr>
<th>Date</th>
<th>Na</th>
<th>K</th>
<th>Mg</th>
<th>Cl</th>
<th>Na/K Ratio</th>
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<td>1966</td>
<td>1966</td>
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<td></td>
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<td>21</td>
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<td>5-2</td>
<td>1-72</td>
<td>103</td>
<td>26</td>
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<td></td>
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<td>2-25</td>
<td>102</td>
<td>—</td>
</tr>
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<tr>
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<td>2-21</td>
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<tr>
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<td>2-27</td>
<td>100</td>
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Results

Serial determinations of serum magnesium and other electrolytes (Table). In the untreated patient (Case 1), who had been given sodium chloride alone 5 days previously, initial serum levels of magnesium and potassium were high whereas serum sodium level was low. After the administration of cortisol, 10 mg. daily, and single intramuscular injection of DOC-trimethylacetate, 20 mg., the serum magnesium level was reduced to normal as the serum sodium level increased. The serum potassium level, on the other hand, dropped abruptly to normal on the 5th day of treatment with mineralocorticoid.
Serum Magnesium Level in the Salt-losing Type of Congenital Adrenal Hyperplasia

**Case 2**

<table>
<thead>
<tr>
<th>Sodium chloride (g./day orally)</th>
<th>Cortisol (mg./day orally)</th>
<th>DOC-Trimethylacetate (mg. i.m.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-0</td>
<td>3-0</td>
<td>8.75</td>
</tr>
<tr>
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<tr>
<td>10</td>
<td>15</td>
<td>25</td>
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</tbody>
</table>

**FIG. 2.—Clinical course of Case 2.**

In the inadequately treated patient (Case 2), who had been treated as congenital adrenal hyperplasia for about 4 months but was poorly controlled with small amounts of DOCA pellets (33 mg.) given 63 days before the start of the study and the oral administration of cortisol, 10 mg. daily, and various amount of salt supplement, serum levels of Na, K, and Mg ranged from 130 to 140 mEq/l., 3·7 to 5·2 mEq/l., and 1·89 to 2·74 mEq/l., respectively.

**Relationship of serum magnesium to other electrolytes (Fig. 3, 4, and 5).** In Case 1, serum magnesium levels were directly proportional to serum potassium, and inversely proportional to serum sodium and Na/K ratios.

In Case 2, serum magnesium was inversely correlated with serum sodium \( r = 0.70, p < 0.01 \). Serum magnesium, on the other hand, showed no significant relation to serum potassium or Na/K ratio. There was, however, a direct correlation between serum magnesium and potassium \( r = 0.80; p < 0.05 \), and an inverse correlation between serum magnesium and Na/K ratio \( r = -0.88; p < 0.05 \) in the hyponatraemic condition (serum sodium level was lower than 135 mEq/l.).

**Discussion**

Magnesium metabolism is complex compared with other electrolytes, and the precise mechanism...
FIG. 3.—Relation of serum magnesium (●) and potassium (○) to serum sodium levels.

FIG. 4.—Relation of serum levels of magnesium and potassium. Solid circles (●) indicate values in the hyponatraemic condition, and open circles (○) in the normonatraemic condition.

FIG. 5.—Relation of serum magnesium levels to Na/K ratios. Symbols as in Fig. 4.
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of the renal excretion of this ion has not been determined (Hills et al., 1955; Womersley, 1956; Jabir, Roberts, and Womersley, 1957; Chesley and Tepper, 1958; Ginn et al., 1959; Barker, Elkinton, and Clark, 1959; Hills et al., 1959). In recent years, therefore, attention has been directed to the effects of hormones such as aldosterone, parathormone, vasopressin, and so on, which play an important role in the renal excretion of magnesium.

Harrop et al. (1933) and Zwemer and Sullivan (1934) reported high serum levels of magnesium in adrenalectomized rats. Thereafter, it was confirmed by Conway and Hingerty (1946), Hingerty (1957), and Weil and State (1958). Mader and Iseri (1955), Milne et al. (1957), and Horton and Biglieri (1962), on the other hand, observed very low levels of serum magnesium and a concomitant increase in the urinary excretion of magnesium in primary aldosteronism. It has been fairly well established that aldosterone increases the renal excretion of magnesium.

In our patients with congenital adrenal hyperplasia the serum magnesium levels were raised, as was the serum potassium, and there were lowered sodium levels in the untreated condition. Serum levels of these cations were corrected by the administration of mineralocorticoids.

The mechanism by which renal excretion of magnesium is carried out is poorly understood. In primary aldosteronism the mechanism of the hypomagnesaemia is a matter of speculation. Magnesium waste in this condition was ascribed by Mader and Iseri (1955), Miller, Faloon, and Lloyd (1958), and Hills et al. (1959) to an intrinsic tubular defect constituting an additional pathophysiological feature of kaliopenic nephropathy, while Hanna and MacIntyre (1960) considered that hypomagnesaemia was not due to kaliopenic nephropathy, but to the direct effect of aldosterone itself.

The present study of serum electrolytes in CAH revealed that the serum magnesium level was high before the serum sodium and chloride were corrected; and the administration of mineralocorticoids resulted in drastic lowering of serum magnesium and potassium with the correction of serum sodium. With regard to the relationships of these cations, there was an inverse correlation between serum magnesium and sodium, and serum magnesium showed a direct correlation with serum potassium and an inverse one with serum Na/K ratio only when there was hyponatraemia. Based on these findings, the following conclusions were drawn: mineralocorticoids reduced serum magnesium level when serum levels of sodium and chloride were corrected, and the effects of mineralocorticoids on serum magnesium and potassium were similar in mineralocorticoid deficiency in man. Further studies on this problem are thought to be necessary.

Summary

Serial determinations of serum magnesium and other electrolytes (Na, K, and Cl) were carried out in two infants with the salt-losing type of congenital adrenal hyperplasia (21-hydroxylase deficiency) treated with salt supplement and combined administration of mineralo- and glucocorticoids. Serum magnesium and potassium levels which were raised in the untreated condition returned to normal after the administration of DOC-trimethylacetate with parallelism. Serum magnesium levels were inversely proportional to serum sodium levels. In the hyponatraemic condition serum magnesium levels showed a direct correlation with serum potassium and an inverse one with serum Na/K ratios. It is strongly suggested that mineralocorticoids reduce serum magnesium level when serum sodium and chloride are corrected, and that the effects of mineralocorticoids on serum magnesium and potassium are very similar in mineralocorticoid deficiency in man.

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