Serum Electrolyte and Acid Base Composition in Patients with Graded Degrees of Chronic Renal Failure

Ho Yung Lee, M.D., Hyon Young Joo, M.D. and Dae Suk Han, M.D.

One hundred sixty-three patients with graded degrees of uncomplicated stable chronic renal failure were studied to investigate the quantitative relationship between serum acid-base and electrolyte composition and serum creatinine level. Even in patients with a mild degree of renal failure, the serum total carbon dioxide (tCO₂) content was reduced significantly. Progressive decrements in tCO₂ were noted in the more severe degrees of renal failure with the reciprocal relationship between tCO₂ and serum creatinine concentration. Depending upon the degree of chronic renal failure, the type of metabolic acidosis was different. In patients with a moderate degree of renal failure, hyperchloremic acidosis was noted with anion gap remaining normal. As the renal failure progressed to a more severe degree, this pattern of hyperchloremic acidosis changed to anion gap acidosis with a normal serum chloride level. The highest anion gap was 25 mEq/L in the patient with serum creatinine concentration 24.7 mg/dL.

Key Words: Chronic renal failure, hyperchloremic acidosis, anion gap acidosis

Metabolic acidosis is an inevitable complication in chronic renal failure (CRF) as a consequence of the diminished functioning renal mass being unable to excrete the daily load of hydrogen ion in the form of ammonium and titratable acid.

It has long been known that patients with CRF due to tubulointerstitial disease develop hyperchloremic acidosis, while anion gap acidosis is the typical pattern in CRF due to glomerular disease. Previous attempts to find the quantitative relationship between the severity of renal failure and the degree of metabolic acidosis have provided no consistent conclusion due to the inadequate design of the studies (Elkinton and Danowski, 1955; Elkinton, 1962). However, according to the report by Widmer and co-workers (1979), the pattern of acid-base disturbance evolves in a consistent fashion as the renal function deteriorates.

The data from 163 patients with uncomplicated stable chronic renal failure was analyzed in order to determine 1) the sequential pattern of metabolic acidosis in relation to the severity of chronic renal failure, 2) the degree of renal failure to develop hyperkalemia and 3) the maximal value of anion gap attainable in severe degree renal failure.

MATERIAL AND METHODS

All medical records of patients with chronic renal failure who had been evaluated either as inpatients or outpatients at Yonsei University Medical Center between Jan. 1979 and Jan. 1984 were used for this study. All patients included in this study were over 15 years of age at the time of evaluation.

The criteria for inclusion in this study were a serum creatinine concentration greater than 1.5 mg/dL on at least two occasions and also the creatinine level increasing progressively without improvement during regular follow-up to select only chronic renal failure. However, in order to be sure that data were included for analysis only from periods in which the level of renal function was known to be stable, we eliminated all observations obtained when serial values for serum creatinine changed at a rate greater than 1.0 mg/dL/mo.
The patients with a history suggesting volume contraction as diarrhea and vomiting or the patients receiving medication known to change the electrolytes and acid-base balance such as diuretics, steroids, or potassium-exchange resins were excluded. The patients with a history of multiple myeloma, adrenalecctomy, or parathyroidectomy were also excluded. Patients otherwise were included in this study in a random manner.

One hundred sixty-three patients who satisfied the above criteria were chosen for this study and divided into three subgroups on the basis of initial serum creatinine level at the time of evaluation: mild (serum creatinine, 1.5-3 mg/dL), moderate (serum creatinine, 3-6 mg/dL) and severe (serum creatinine, greater than 6 mg/dL) renal failure group.

Twelve patients without renal disease with a serum creatinine level less than 1.5 mg/dL were selected for the control group using the same exclusion criteria as the renal failure groups. Patients were included in the control and renal failure groups only if serum creatinine and serum electrolytes were obtained simultaneously.

The serum anion gap defined in mEq per liter by the formula: Anion gap = (Na)−[(Cl−)+(HCO3−)] was calculated in each patient in the control and renal failure groups.

All determinations were performed on venous blood by the clinical laboratory of Yonsei University Medical Center. Serum electrolytes and creatinine were measured by standard method as adopted for an automated blood chemical analyzer using ASTRA TM-8 (Beckman, USA).

Comparisons among groups were performed using student's test.

RESULTS

Table 1 shows clinical characteristics of the patients in each subgroup. There was no significant difference in the mean age of each group: control group, 47.4±12.2 years, mild group 46.2±16.5 years, moderate group 46.7±14.4 years, and severe group 42.0±14.1 years. The sex ratio was also very similar in each renal failure subgroup.

Table 2 shows details of the serum electrolyte concentrations and anion gaps of the control and renal failure subgroups. No significant difference in serum sodium concentration was seen among the study groups. There was no significant difference in the serum potassium level between the control and mild renal failure group; but in the moderate and severe renal failure groups, significantly elevated potassium levels were noted. The serum chloride concentration in moderate renal failure group was also definitely

<table>
<thead>
<tr>
<th>Table 1. Characteristics of study groups</th>
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<tbody>
<tr>
<td>Group</td>
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</tr>
<tr>
<td>Control Group</td>
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<td>Mild Group</td>
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<td>Moderate Group</td>
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<td>Severe Group</td>
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* Values shown are mean ± S.D.

<table>
<thead>
<tr>
<th>Table 2. Serum electrolyte concentration in control and renal failure groups*</th>
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<tbody>
<tr>
<td>Group</td>
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<td>Control Group</td>
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<td>Severe Group</td>
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* values shown are mean ± S.D.; all measurements are mEq/L
+ significantly different from control (P<0.005)
▲ significantly different from control (P<0.05)
(N) No. of cases
Table 3. Serum tCO₂ and serum anion gap concentration in graded degrees of creatinine

<table>
<thead>
<tr>
<th>Serum Creatinine, (mg/dl)</th>
<th>Serum tCO₂, (mEq/l)</th>
<th>Serum Anion Gap, (mEq/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 (33)</td>
<td>24.0±3.5</td>
<td>11.0±4.4</td>
</tr>
<tr>
<td>3- 6 (34)</td>
<td>20.1±5.0▲</td>
<td>10.8±4.8</td>
</tr>
<tr>
<td>6- 9 (29)</td>
<td>17.8±4.0</td>
<td>13.1±5.4▲</td>
</tr>
<tr>
<td>9-12 (23)</td>
<td>17.3±4.0</td>
<td>15.3±5.3</td>
</tr>
<tr>
<td>12-15 (22)</td>
<td>16.8±5.0</td>
<td>16.1±4.3</td>
</tr>
<tr>
<td>15-18 (16)</td>
<td>16.1±5.5</td>
<td>18.6±4.9</td>
</tr>
<tr>
<td>≥18 (18)</td>
<td>15.0±5.4</td>
<td>20.5±4.5</td>
</tr>
</tbody>
</table>

* Values shown are mean ± S.D.
▲ p < 0.05
(N) No. of cases

could be seen between the serum total CO₂ content and serum creatinine concentration in all of the renal failure study groups (Table 3, Fig. 1).

The mean serum anion gaps calculated in the mild and moderate renal failure groups were not significantly different from those observed in the control group. However, the mean serum anion gap in the severe renal failure group was definitely higher than in the control groups or the more mild renal failure groups (Table 2). As can be seen in Table 3, the serum anion gap tended to increase progressively as the serum creatinine level was elevating.

Figure 2 shows the relationship of serum anion gap to serum creatinine concentration in control patients and in patients with graded degrees of renal failure. The anion gap concentration ris ed progressively as the severity of the renal failure progressed.

**DISCUSSION**

Net daily acid load of 50 to 100 mEq has to be cleared from the kidney to maintain normal acid-base balance. In chronic renal failure, tubular damage induces hypobicarbonatemia by reduced hydrogen excretion and bicarbonate production. Concomitant glomerular failure results in retention of acid anions. The net result of these two pathologic processes and
their parallel progression is the high anion gap metabolic acidosis which is the characteristic pattern in chronic renal failure.

Early stage renal failure usually does not develop metabolic acidosis because of increased ammoniagenesis and acid excretion in the remaining functional nephron (Narins, 1978). A recent study suggests that hypertrophy of the remaining tubular epithelium brings about an increased production of ammonia per residual nephron (MacLean and Hayslett, 1980).

Traditional teaching indicates that chronic tubulointerstitial disease usually develops early onset of hyperchloremic acidosis; but several attempts to prove this have yielded no consistent findings (Elkinton, 1962; Johnson and Morgan, 1965; Elkinton, 1966).

In this study, we found hyperchloremic acidosis with anion gap remaining normal in moderate renal failure, but the pattern of acidosis changed to high anion gap acidosis with no more hyperchloremia as the renal failure progressed to a more severe degree (Table 2). In a retrospective analysis of 41 patients with graded degrees of chronic renal failure, Widmer et al. (1979) reported that a moderate degree of renal failure was associated with hyperchloremic acidosis but as the severity of renal failure progressed, this pattern of hyperchloremic acidosis tended to give way to high anion gap acidosis with the serum chloride concentration remaining at the high level achieved during moderate renal failure. This did not agree with our results. The reason for the discrepancy between our results and Widmer's in the pattern of the metabolic acidosis in severe degree renal failure is not clear. A more prospective study with large numbers of patients may be needed to define the acidosis pattern in graded degrees of chronic renal failure.

In a patient with unexplained metabolic acidosis with an increased anion gap, the degree of high anion gap can be helpful in identifying the underlying cause. Patients with an extremely high anion gap greater than 35 mEq/liter usually have ethylene glycol intoxication (Kane, 1968; Underwood and Bennett 1973; Jacobsen et al., 1982), methanol intoxication (Fappas and Silverman, 1982) or lactic acidosis (Fraley et al., 1981; Appel et al., 1983). However, even in patients with a severe degree of chronic renal failure, the anion gap usually remains less than 25 mEq/liter (Gonick et al., 1969; Widmer et al., 1979; Gabow et al., 1980). The highest anion gap noted in our study was 25 mEq/liter in the patient with serum creatinine concentration 24.7 mg/dl (Table 3). It is also of particular note that the increment in serum anion gap in the patients with graded degrees of renal failure is highly correlated
with the increment of serum creatinine level with the correlation coefficient of 0.9 (Fig. 2).

The renal mechanisms responsible for the evolving pattern of acid base and electrolyte imbalance in graded degrees of chronic renal failure are still not clearly understood. In the early stage of chronic renal failure, acid base balance is usually maintained by increased ammonium excretion per residual functioning nephron (Dorhout-Mees et al., 1966; Welbourne et al., 1972). However, total ammonium excretion begins to decrease with the GFR is less than 40 to 50 ml/min (Schwartz et al., 1959), suggesting that maximal ammonium production in fewer functioning nephrons is below the requirement (Welbourne et al., 1972). Decreased titrable acidity may also contribute to renal acidosis in these patients with chronic renal failure (Schwartz et al., 1959).

An additional factor may be bicarbonate wasting due to the combined effect of tubular damage, solute diuresis and secondary hyperparathyroidism which impairs bicarbonate reabsorption in proximal tubules (Schwartz et al., 1959). Widmer et al. (1979) suggested that enhanced chloride reabsorption due to an increased level of poorly reabsorbable anion in the tubular lumen plays a critical role in the metabolic acidosis of moderate renal failure.

Relative free water excretion, as measured by C\textsubscript{H2O}/GFR, is usually normal in renal failure (Kleeman et al., 1961); but in severe renal failure, there is a proportionate decrease in loop delivery and free water clearance (C\textsubscript{H2O}) resulting in dilutional hyponatremia. However, there was no significant hyponatraemia in our study, even in patients with severe renal failure (Table 2).

Potassium balance is usually maintained in the early stage of chronic renal failure through the increased potassium excretion per functioning nephron and the colon by aldosterone induced increase in Na-K-ATPase activity as long as urine output remains adequate (Bastl et al., 1977). We noted normal serum potassium concentration in the patients with mild renal failure, but a significant elevation of serum potassium concentration was noted in the patients with moderate and severe renal failure (Table 2).

REFERENCES


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