The Use of L-Lysine Monohydrochloride in Combination with Mercurial Diuretics in the Treatment of Refractory Fluid Retention

By Albert L. Rubin, M.D., Norton Spritz, M.D., Allen W. Mead, M.D., Richard A. Herrmann, M.D., Warren S. Braveman, M.D., and E. Hugh Luckey, M.D.

In patients with fluid retention, a regimen of salt restriction, mercurial agents, and digitalis when indicated usually produces an adequate diuretic response. In many instances, however, these measures become ineffective, and the production of a hyperchloremic acidosis is then necessary to restore responsiveness to a mercurial agent.1

Ammonium chloride or calcium chloride, alone or in combination with the carbonic anhydrase inhibitor, acetazolamide1,2 has been used successfully to produce a hyperchloremic acidosis in such subjects. Both salts have an unpleasant taste, however, and often are limited in their usefulness by severe gastrointestinal side effects. Experience in this laboratory now includes 2 instances of hematemesis associated with administration of calcium chloride. Since most patients with resistant edema have decreased liver function, due either to primary liver disease or to congestive liver disease secondary to long-standing heart failure, administration of ammonium chloride may produce ammonia toxicity. Many instances of this complication have been reported.3,4

Because of these undesirable side effects a search was instituted for a more satisfactory source of the chloride ion. At the suggestion of Dr. Vincent duVigneaud the chlorides of the basic amino acids were examined. A child with refractory edema unable to take ammonium or calcium chloride tolerated L-lysine monohydrochloride well, and subsequently had a good diuretic response to mercurial administration.5 In order further to evaluate the effectiveness of this substance in producing the metabolic effects necessary to reestablish mercurial responsiveness, L-lysine monohydrochloride* was administered to a group of adult patients who had edema resistant to mercurial diuretics. It was found that this material produces an adequate hyperchloremic acidosis without the undesirable side effects of ammonium and calcium chloride.

Materials and Methods

Fourteen patients received L-lysine monohydrochloride in 16 courses of treatment. Each patient had edema, with or without ascites, due either to Laennec's cirrhosis or chronic congestive heart failure. Patients were selected in whom the primary diagnosis was evident from the history, physical findings, and appropriate laboratory determinations. Preceding the use of L-lysine monohydrochloride, all patients had been hospitalized for a control period, during which a combination of fluid and salt restriction, modified bed rest, digitalis when indicated, and daily mercurial diuretics, often in combination with chlorothiazide, were initially ineffective, or had become so, in producing significant weight loss. In 1 patient, calcium chloride, which had been administered to reestablish responsiveness to a mercurial diuretic, had to be discontinued because of gastrointestinal side effects.

*Kindly supplied by the Lysine Division of E. I. du Pont de Nemours and Company, Inc. The product used contains 95 per cent L-lysine monohydrochloride and 5 per cent D-lysine monohydrochloride. This product contains approximately 5 mEq. of chloride ion per gram.
L-lysine monohydrochloride was then administered in a dosage of 10 Gm. 4 times a day, usually in fruit juice immediately following a meal. No diuretic agents were administered during this period and no other changes were made in the therapeutic program. Following this preparatory period a daily injection of a mercurial diuretic was given, continuing the same dose of L-lysine monohydrochloride.

Urine volume and body weight were measured daily in all subjects throughout the study. Urine and plasma electrolyte concentrations and blood pH were frequently determined. The methods used for these determinations are described in a previous publication.1

Results

Table 1 is a compilation of the clinical data, electrolyte changes, and response to therapy in each course during 3 phases of observation: (1) the control period preceding administration of L-lysine monohydrochloride; (2) the period of administration of L-lysine monohydrochloride during which hyperchloremic acidosis was produced; (3) the period during which L-lysine monohydrochloride and mercurial were administered together.

Figure 1
Graphic representation of the data obtained in a patient with Laennec's cirrhosis during the described treatment periods.

Figure 2
Graphic representation of the data obtained in a patient with congestive heart failure during the described treatment periods.

Figure 1 is a graphic presentation of the results in a representative subject with cirrhosis of the liver.

Control Period

The ineffectiveness of the diuretics employed during this period is shown by the constancy of body weight. Patients in whom weight loss is recorded during this period became unresponsive to the diuretics employed and had persistent edema. In patient R. H. calcium chloride was effective in restoring mercurial effect, but had to be discontinued because of nausea and vomiting, and L-lysine monohydrochloride was substituted. Figure 2 records this patient's course.

In those instances in which the initial urine chloride concentration is recorded above 10 mEq./L, a mercurial diuretic had been administered within the preceding 36 hours.

Production of Hyperchloremic Acidosis with L-lysine Monohydrochloride

Following the control period, the patients were given L-lysine monohydrochloride in dosage of 10 Gm., 4 times daily for 2 to 5 days.
### Table 1

**Body Weight, Blood pH, Plasma Carbon Dioxide Combining Power, Plasma, and Urinary Chloride Concentrations in Patients during Various Treatment Periods**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Lassen's cirrhosis</th>
<th>Congestive heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control period</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of days</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Wt. change in lbs.</td>
<td>.25</td>
<td>11</td>
</tr>
<tr>
<td>Urine chloride</td>
<td>6.4</td>
<td>16</td>
</tr>
<tr>
<td>Plasma chloride</td>
<td>105</td>
<td>105</td>
</tr>
<tr>
<td>Venous pH</td>
<td>7.24</td>
<td>7.36</td>
</tr>
<tr>
<td><strong>Lysine alone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of days</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Wt. change in lbs.</td>
<td>.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Urine chloride range (mEq/L)</td>
<td>6-155</td>
<td>15-64</td>
</tr>
<tr>
<td>Plasma chloride</td>
<td>112</td>
<td>115</td>
</tr>
<tr>
<td>CO₂ comb. power range (mMol/L)</td>
<td>16</td>
<td>27-24</td>
</tr>
<tr>
<td><strong>Lysine and Mercurial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of days</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Wt. change in lbs.</td>
<td>-.16</td>
<td>-.135</td>
</tr>
<tr>
<td>Urine chloride range (mEq/L)</td>
<td>217-158</td>
<td>250-200</td>
</tr>
<tr>
<td>Plasma chloride</td>
<td>113</td>
<td>118</td>
</tr>
<tr>
<td>CO₂ comb. power range (mMol/L)</td>
<td>15-17</td>
<td>15-24</td>
</tr>
</tbody>
</table>
During this period significant weight loss did not occur. In all instances, an increase in plasma chloride concentration and a fall in carbon dioxide combining power (as low as 7.6 mEq./L) occurred. Blood pH fell in most instances, the lowest recording being 7.18. In no instance was hyperpnea or any other symptom attributable to the acidosis observed.

An increase in the urine chloride concentration to 40 mEq./L or more was a useful indicator that responsiveness to mercurial administration might be expected. This criterion was based on previous studies in this laboratory. In patients who began receiving L-lysine monohydrochloride within 24 hours following an injection of mercurial diuretic, the initial urine chloride often exceeded 40 mEq./L without a diuresis. In such subjects a further rise of urine chloride concentration of 40 mEq./L or more was used as the indicator of satisfactory hyperchloremia.

**Mercurial Administration Following the Production of Hyperchloremic Acidosis**

In the setting of the hyperchloremic acidosis produced by the administration of L-lysine monohydrochloride, the administration of a mercurial agent was associated with a significant weight loss in all patients studied.

L-lysine monohydrochloride was continued to maintain the hyperchloremia during mercurial administration. The plasma chloride level returned toward normal during the diuresis. Potassium depletion was prevented by the administration of oral potassium chloride in amounts determined by the magnitude of the diuresis. Usually 3 to 6 Gm. of potassium chloride were sufficient.

In most instances the diuretic program was discontinued because a satisfactory clinical response had been produced. In some patients the therapeutic program became ineffective following an initial response, with significant edema or ascites still present. In several such patients the reestablishment of a hyperchloremic acidosis was associated with further mercurial diuretic response and further weight loss.

**Side Effects**

This chloride salt has now been used in our clinical services for more than 2 years. L-lysine monohydrochloride proved to be acceptable to all patients studied. Cold fruit juice was found to be the most satisfactory vehicle for its administration, and the product was given immediately after a meal whenever possible. In no case was the medication refused—a not uncommon occurrence with both ammonium and calcium chloride. No side effects necessitating the discontinuance of L-lysine monohydrochloride have occurred. There has been no instance of gastrointestinal bleeding associated with its administration.

Diarrhea was the only side effect noted, and it was never severe enough to require discontinuing the L-lysine monohydrochloride. In 1 instance diarrhea that had occurred in one course of treatment did not recur during a second.

Many of the patients had far advanced impairment of liver function at the time of study. In no instance was development of flapping tremor, mental change, or other significant clinical deterioration noted as a result of L-lysine monohydrochloride administration.

Frequent urinalyses and blood urea and hematologic studies revealed no evidence of renal or hematopoietic toxicity.

**Discussion**

L-lysine monohydrochloride is a salt of a naturally occurring amino acid with a molecular weight of 195. It has been used in commercial food and vitamin preparations, and no human toxicity has been reported. In animal studies, large amounts of L-lysine monohydrochloride, administered in a setting of specific deficiency of other amino acids, have been associated with interference with optimal growth. The experimental conditions in these animal studies were extreme, and actually have no clinical counterpart in these studies. Five-gram doses of L-lysine monohydrochloride administered to normal adults produced measurable increases in gastric peptic activity without producing gastrointestinal symptoms. It would therefore appear...
advisable to insure adequate protein intake in subjects given L-lysine monohydrochloride in the amounts needed for adequate hyperchloremia, and to use caution in patients in whom increased peptic activity represents an added risk. In no instance, however, has activation of peptic ulcer disease or bleeding from esophageal varices occurred. It should be noted that the daily dosages employed in this study were 40 to 80 times as large as the quantities normally employed when L-lysine monohydrochloride is given as a dietary supplement.\(^9\)

In these patients selected on the basis of resistance to usual diuretic regimens, L-lysine monohydrochloride alone, as would be expected, did not produce a diuretic effect in patients with milder degrees of fluid retention; however, it is probable that L-lysine monohydrochloride in smaller doses will be a useful diuretic drug when given alone as well as in association with mercurial diuretics.

The production of a hyperchloremic acidosis by the method described should be reserved for refractory fluid retention states. It must be emphasized that its application requires close clinical observation and frequent pertinent laboratory examinations in order to avoid the potentially serious consequences of a severe metabolic acidosis. It is a program that we believe should be undertaken only in the hospitalized patient.

**Summary**

Administration of large doses of L-lysine monohydrochloride at meal times has proved to be an efficient method, free of significant side effects, for the production of a hyperchloremic acidosis to restore responsiveness to mercurial diuretics in cardiac and cirrhotic patients with refractory fluid retention. Results obtained in a group of 14 patients are presented and advantages of L-lysine monohydrochloride over previously available acidifying chloride salts are discussed.

**Acknowledgment**

The authors express their appreciation to the following research fellows who assisted in these studies: Burton D. Cohen, M.D., Glenn D. Lubash, M.D., and David Brailovsky, M.D.

**Sumario in Interlingua**

Le administration de grande doses de monohydrochloruro de L-lysina al tempore del repastos se ha manifestate efficace—sin significativa effetos lateral—in producere un acidose hyperchloremica pro restaurare le responsivitate a diureticos mercurial del parte de patientes con retention refractori de liquido. Es presentate le resultatos obtenite in un serie de 14 patientes. Le avantages de monohydrochloruro de L-lysina es discutite in comparation con previemente disponibile chloruros acidificanti.

**References**

5. Goldberg, H.: Personal communication.
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doi: 10.1161/01.CIR.21.3.332

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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http://circ.ahajournals.org/content/21/3/332