Effectiveness of an Oral, Nonmercurial Diuretic:
Clinical Trial with Thirty-Five Patients

By Benjamin Wainfeld, M.D., Jacob J. Yarvis, M.D., and I. Richard Schwartz, M.D.

In a previous trial of aminometramid on 30 patients with peripheral edema, 19 became refractory to the drug. These 19 patients and another group of 16 with peripheral edema or ascites were placed on another nonmercurial diuretic aminoisometradine, which had shown promise in previous studies in animals and man. This group of 35 patients who had previously required frequent injections of mercurial diuretics were treated with the new diuretic for at least 8 months. Conclusions of this study are presented.

In a previous report, dealing with the clinical evaluation of aminometramid (Mictine) in a group of 30 patients with peripheral edema due to congestive heart failure, 19 patients who had responded well at the outset developed resistance to the action of the drug after 5 to 20 weeks of therapy. These 19 patients were then given another nonmercurial diuretic drug, a derivative of pyrimidinedione, known as aminoisometradine (Rolicton).* The initial response of this group of 19 patients to the new drug appeared promising and another study was organized to include these patients plus a new group of patients with congestive heart failure. Five patients with ascites and edema caused by Laennee's cirrhosis were also added to the study.

Impetus was given to our efforts to find a satisfactory nonmercurial diuretic by the presence of over 150 patients weekly at the diuretic injection clinic at this hospital. Problems associated with long-term therapy involving mercurial diuretics are well known and have been amply discussed in the literature. It was therefore believed that a satisfactory nonmercurial drug would be of great value in the management of patients in whom the use of organomercurials was deemed inadvisable for one reason or another.1

Materials and Methods

The group of 19 patients who had been receiving Mictine together with the new group of 16 patients were evaluated anew. They were all patients who had required weekly or biweekly injections for at least 6 months. They were screened for a 4-week period. All nonmercurial diuretic therapy was withheld, they were examined and weighed biweekly, and mercurial diuretic agents were administered as indicated by their clinical state. In this manner their individual requirements for medication were established. The group consisted of 35 patients who attended clinic regularly and participated in the study for at least 8 months. A few additional patients entered and left the study during this time but are not included because of insufficient observation. The criteria used in determining diuretic requirements were signs of weight gain, peripheral edema, pulmonary congestion, hepatic enlargement, and subjective symptoms of dyspnea and orthopnea. These also served as standards in evaluating success or failure of therapy. The age, diagnosis, and other pertinent data are given in table 1.

Each patient had a 6-foot roentgen film of the chest and a 12-lead electrocardiogram. In addition, levels of serum sodium, potassium, chlorides, and blood urea nitrogen were determined. These were used as a baseline in determining the biochemical effects of the diuretic agent under study. The examinations listed above were repeated periodically and the patients were observed initially and at last biweekly thereafter. At each visit special attention was paid to weight gain or loss and to the existence of peripheral edema. Heart and lungs were examined routinely and any dyspnea, orthopnea, or symptoms of toxicity were noted.

They were then given Rolicton, which was obtainable only at each clinic visit. The dosage varied from 400 mg. to 5 Gm. daily and was changed as the patient's clinical condition required.

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*The supply of Rolicton was kindly given by Dr. J. William Crosson, Assistant Director, Clinical Research, G. D. Searle & Co., Inc., Chicago, Ill.
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Table 1.—Clinical Data on Thirty-Five Patients

<table>
<thead>
<tr>
<th>Patient no., age, sex</th>
<th>Diagnosis</th>
<th>Number of injections per week</th>
<th>Dose Rolicon (Gm.)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 51, M</td>
<td>ASHD, Laennec’s cirrhosis</td>
<td>1</td>
<td>1.2</td>
<td>Good, injections spaced out 10-14 days</td>
</tr>
<tr>
<td>2. 53, F</td>
<td>RHD, Hyperthyroidism</td>
<td>2</td>
<td>5.0</td>
<td>Poor</td>
</tr>
<tr>
<td>3. 42, M</td>
<td>RHD</td>
<td>1</td>
<td>1.6</td>
<td>Good, injections spaced out 10-14 days</td>
</tr>
<tr>
<td>4. 41, M</td>
<td>ASHD</td>
<td>1</td>
<td>0.8</td>
<td>Excellent, no further injections</td>
</tr>
<tr>
<td>5. 61, F</td>
<td>ASHD</td>
<td>1</td>
<td>0.8</td>
<td>Good, injections spaced out 10-12 days</td>
</tr>
<tr>
<td>6. 47, M</td>
<td>RHD</td>
<td>1</td>
<td>1.0</td>
<td>Excellent, no further injections</td>
</tr>
<tr>
<td>7. 71, M</td>
<td>ASHD</td>
<td>1</td>
<td>1.2</td>
<td>Good, injections spaced out 10-14 days</td>
</tr>
<tr>
<td>8. 51, M</td>
<td>RHD</td>
<td>2</td>
<td>5.0</td>
<td>Poor</td>
</tr>
<tr>
<td>9. 68, M</td>
<td>Cor Pulmonale, chronic pulmonary disease</td>
<td>2</td>
<td>2.0</td>
<td>Good, injections spaced out 6-10 days</td>
</tr>
<tr>
<td>10. 67, M</td>
<td>ASHD, Diabetes mellitus</td>
<td>1</td>
<td>1.6</td>
<td>Good, injections spaced out 10-14 days</td>
</tr>
<tr>
<td>11. 53, M</td>
<td>ASHD</td>
<td>1</td>
<td>1.2</td>
<td>Excellent, no further injections</td>
</tr>
<tr>
<td>12. 61, M</td>
<td>ASHD</td>
<td>1</td>
<td>1.2</td>
<td>Excellent, no further injections</td>
</tr>
<tr>
<td>13. 42, M</td>
<td>RHD</td>
<td>2</td>
<td>5.0</td>
<td>Pair, injections spaced out 7-10 days</td>
</tr>
<tr>
<td>14. 48, M</td>
<td>ASHD</td>
<td>1</td>
<td>1.2</td>
<td>Very good, injections spaced 18-21 days</td>
</tr>
<tr>
<td>15. 69, M</td>
<td>ASHD, HHD</td>
<td>1</td>
<td>1.6</td>
<td>Good, injections spaced out 10-14 days</td>
</tr>
<tr>
<td>16. 63, M</td>
<td>ASHD</td>
<td>1</td>
<td>1.2</td>
<td>Excellent, no further injections</td>
</tr>
<tr>
<td>17. 66, M</td>
<td>HHD</td>
<td>1</td>
<td>1.6</td>
<td>Excellent, no further injections</td>
</tr>
<tr>
<td>18. 74, M</td>
<td>ASHD</td>
<td>1</td>
<td>1.2</td>
<td>Excellent, no further injections</td>
</tr>
<tr>
<td>19. 67, F</td>
<td>ASHD</td>
<td>1</td>
<td>0.8</td>
<td>Excellent, no further injections</td>
</tr>
<tr>
<td>20. 68, M</td>
<td>ASHD</td>
<td>1</td>
<td>0.8</td>
<td>Excellent, no further injections</td>
</tr>
<tr>
<td>21. 57, F</td>
<td>HHD</td>
<td>1</td>
<td>1.2</td>
<td>Excellent, no further injections</td>
</tr>
<tr>
<td>22. 63, M</td>
<td>ASHD</td>
<td>2</td>
<td>1.6</td>
<td>Good, injections spaced out 10-12 days</td>
</tr>
<tr>
<td>23. 38, F</td>
<td>ASHD</td>
<td>2</td>
<td>5.0</td>
<td>Poor</td>
</tr>
<tr>
<td>24. 74, M</td>
<td>ASHD</td>
<td>1</td>
<td>1.2</td>
<td>Good, injections spaced out 10-14 days</td>
</tr>
<tr>
<td>25. 44, F</td>
<td>RHD</td>
<td>1</td>
<td>1.2</td>
<td>Good, injections spaced out 10-14 days</td>
</tr>
<tr>
<td>26. 55, M</td>
<td>HHD</td>
<td>1</td>
<td>0.8</td>
<td>Excellent, no further injections</td>
</tr>
<tr>
<td>27. 62, F</td>
<td>ASHD</td>
<td>2</td>
<td>5.0</td>
<td>Poor</td>
</tr>
<tr>
<td>28. 53, F</td>
<td>RHD</td>
<td>2</td>
<td>5.0</td>
<td>Poor</td>
</tr>
<tr>
<td>29. 61, F</td>
<td>ASHD</td>
<td>1</td>
<td>0.8</td>
<td>Excellent, no further injections</td>
</tr>
<tr>
<td>30. 49, M</td>
<td>ASHD</td>
<td>1</td>
<td>1.0</td>
<td>Good, injections spaced out 14 days</td>
</tr>
<tr>
<td>31. 42, M</td>
<td>Laennec’s cirrhosis</td>
<td>2</td>
<td>5.0</td>
<td>Poor</td>
</tr>
<tr>
<td>32. 58, M</td>
<td>Laennec’s cirrhosis</td>
<td>2</td>
<td>5.0</td>
<td>Poor</td>
</tr>
<tr>
<td>33. 64, F</td>
<td>Laennec’s cirrhosis</td>
<td>2</td>
<td>5.0</td>
<td>Poor</td>
</tr>
<tr>
<td>34. 56, M</td>
<td>Laennec’s cirrhosis</td>
<td>2</td>
<td>5.0</td>
<td>Slight reduction in ascites and edema</td>
</tr>
<tr>
<td>35. 61, M</td>
<td>Laennec’s cirrhosis</td>
<td>2</td>
<td>2.0</td>
<td>Moderate reduction in ascites and edema</td>
</tr>
</tbody>
</table>

RHD—rheumatic heart disease; ASHD—Arteriosclerotic heart disease; HHD—hypertensive heart disease

RESULTS AND CONCLUSIONS

Two patients who had not responded to Mictine, cases 2 and 8, and who required bi-weekly mercurial injections did not respond to Rolicon either. The daily dose was increased to 5 Gm. in each case with no result; even at the maximum dose, no sign or symptom of toxicity was elicited. The patients continued to require mercurial injections as before. Of the remaining 17 patients who were transferred from Mictine to Rolicon, 9 responded well from the outset. They were maintained free of edema, with no further mercurial injections required for periods up to 32 weeks. The remaining 8 patients appeared to respond for periods ranging from 2 to 8 weeks, but then began to require mercurial injections again. However, whereas they had required weekly injections, these were now spaced out over 10 to 14 day periods. In 1 case, case 14, injections are now required about once in 18 to 21 days.

Of the 11 patients who previously had not received any oral drug, those responded best who had required injections once weekly or less frequently. Four patients no longer re-
quired injections at all, another 4 had their injections spaced out over longer periods of time. Three patients in severe congestive heart failure and requiring injections biweekly responded poorly. The patients who responded well were free of edema, show no sign of weight gain, and subjectively feel as well as they did with mercurial agents.

The patients with Laennec's cirrhosis showed only moderate response to the drug. Only 2 of the 5 patients studied showed any loss in weight and in ascites and peripheral edema. The remaining 3 gave no sign of improvement in their state.

Repeated biochemical studies revealed no significant changes from the baseline levels established at the start of the study and there were no symptoms of toxicity reported. The drug was uniformly well tolerated. It was found that if a total daily dose of 2 Gm. was insufficient to control fluid retention, little was gained by further increase in dose. Doses as high as 5 Gm. daily were well tolerated.

Inasmuch as patients with severe congestive failure requiring frequent mercurial injections were not benefited to any degree, it appears premature to conclude that a satisfactory nonmercurial oral diuretic has been obtained. The problem of fluid retention is still with us and continued search for an oral diuretic effective in advanced failure is warranted.

The optimum dose varied with each patient. It was found that 800 mg. to 1.6 Gm., 2 to 4 tablets in divided doses daily, were usually satisfactory. There was no special need to take the drug with meals.

**Summary**

Thirty-five patients with fluid retention caused by heart disease and Laennec's cirrhosis were studied in a clinical evaluation of Rolicton. Thirteen showed an excellent response to the drug, remaining comfortable clinically with no fluid retention at the end of 32 weeks of therapy. Eleven patients continue to require mercurial injections but these have been spaced out over longer periods of time. One patient requiring weekly injections is now controlled by 1 injection every 18 to 21 days. Five patients with severe congestive failure requiring 2 injections weekly were not benefited to any degree. Of 5 patients with Laennec's cirrhosis, 2 responded to treatment with a reduction in ascites and edema while 3 showed no response. No signs of biochemical abnormalities were demonstrated after repeated laboratory studies, and toxicity to the drug was not present in any patient. The optimum dose must be individualized for each patient but was found to lie between 800 mg. and 1.6 Gm. daily in divided doses. The drug appears to warrant a trial in cases of mild to moderately severe fluid retention due to congestive heart failure. It is of limited value in cases of severe congestive heart failure with extreme fluid retention. In all cases where mercurial therapy is contraindicated, clinical trial of the drug appears warranted.

**Summario in Interlingua**

Trenta-cinque patientes con retension de fluido causate per morbo cardiae e cirrhosis de Laennec esseva studiate in un evaluation clinic de Rolicton. Dece-tres mostrava un excellent responsa al droga. Illes se manteneva in un stato de comfortabilitate clinic sin retension de fluido al fin de un curso therapeutic de 32 septimanas. Dece-un patientes continua requirer injectiones de mercurial, sed iste injectiones es separate per plus longe intervallos. Un patiente qui requireva injectiones septimanal es nunc mantenite per un injection omne 18 a 21 dies. Cinque patientes con sever disfallimento congestive, qui requireva 2 injectiones per septima, non beneficiava a grados significative. Ex le 5 patientes con cirrhosis de Laennec, 2 respondeva per un reduction del ascites e del edema, durante que le 3 alteres monstrava nulle responsa. Nulle signos de anormalitate biochimic esseva demonstrate per repetite studios laboratorial, e toxicitate como effecto del droga non esseva constatate in ulla del pacientes. Le dosage optimal debe esser determinate pro omne patiente individual, sed il
AN ORAL, NONMERCURAL DIURETIC

esseva trovate que illo es inter 800 mg e 1,6 g per die in doses dividite. Il pare que le droga merita esser essayate in casos de leve o moderate retention de fluido attribuibile a congestive disfallimento cardiac. Illo es de pauc valor in casos de sever disfallimento cardiac congestive con extreme grados de retention de fluido. In omne casos in que un therapia mercurial es contraindicate, le essayo clinic del droga pare esser justificate.

REFERENCES


In 3 sets of experiments in rabbits, an attempt was made to induce arteriosclerotic changes in pulmonary vessels. It was postulated that repeated emboli caused arteriosclerotic changes, not through organization of emboli, but through repeated arteriospasm and resultant changes in the nutrition of cells in the walls of the vessels because the blood supply was diminished. The experiments were, therefore, designed to induce spasm in the pulmonary vessels. To insure organization, repeated pulmonary air emboli were induced in 1 group of rabbits. Repeated air emboli induced changes compatible with arteriosclerosis in the pulmonary vessels. Arteriospasm was observed in the control animals at the time air emboli were induced. To cause spasm of vessels without emboli, adenosine-triphosphate was injected into another group of rabbits, and although spasm occurred, no arteriosclerotic changes were induced. In a third group of animals, the left pulmonary artery was ligated and emboli were induced in the right lung to see if any hormonal or reflex changes in the left lung resulted, which could cause arteriosclerotic changes. There was no evidence that any arteriosclerotic changes were induced by reflex or hormonal action.

Harvey
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