Clinical Evaluation of a New Oral Nonmercurial Diuretic

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The oral administration of the organomercural drugs in patients requiring prolonged management of congestive failure has been rather unsatisfactory because of occasional toxic signs and symptoms. With the development of the pyrimidinedione derivatives as diuretic agents and encouraging pharmacologic studies in animals, clinical trial is warranted. A group of 24 patients who had received injections of mercurial diuretics for at least 6 months prior to study were treated with this new diuretic. Results of this experience are described.

The problems associated with long-term therapy involving mercurial diuretics have been thoroughly discussed in recent medical literature. The occasional toxic signs and symptoms reported and the pain and inconvenience of repeated injections further emphasize the desirability of finding an effective oral diuretic. Many patients requiring diuretic therapy present evidence of renal failure of varying degree, and the use of the organomercural drugs is not desired in some of these. A satisfactory nonmercurial drug would therefore be of great value in the management of such patients.

The development of the pyrimidinedione derivatives as diuretic agents, and the preliminary pharmacologic studies in animals, seemed to indicate that a clinical trial was warranted. Perhaps a further incentive to such a clinical investigation was the presence of over 150 patients weekly at the diuretic injection clinic at this hospital.

Material and Methods

In an effort to conduct a valid study, the patients reporting weekly or biweekly for their injections were screened for a period of 1 month. Only those patients who had received injections for at least 6 months prior to our study were considered. During this month of observation all diuretic therapy was withheld and the patients were weighed biweekly. In this manner their individual requirements for medication were established. A group of patients was chosen who required at least 1 injection of a mercurial diuretic each week; frequently they required 2.

This group consisted of 30 patients, but only 24 are to be discussed. The remaining 6 patients attended at infrequent intervals or dropped out of the study early in its course. Each of these 24 patients had required at least 1 mercurial injection weekly for 6 months prior to screening, and also during the 4-week screening period. The criteria used in determining diuretic requirements were signs of weight gain, peripheral edema, pulmonary congestion, and hepatic engorgement and subjective symptoms of dyspnea and orthopnea. These manifestations also served as standards in evaluating success or failure of therapy during the study. The age, diagnoses, and other pertinent data are given in table 1.

Each patient had a 6-foot x-ray film of the chest and a 12-lead electrocardiogram. In addition, the serum sodium, potassium, chlorides, and blood urea nitrogen levels were determined. These were used as a baseline in the study of the effect of the diuretic agent being evaluated. Since the patients were drawn from an ambulatory clinic population, the measure of effective diuretic activity was a careful determination of the weight at each visit. The examinations listed above were also repeated periodically at stated intervals. The patients were observed initially and at least biweekly thereafter by one of us. At each visit special attention was paid to weight gain or loss and to the presence or absence of peripheral edema, the lungs and heart were examined routinely, and symptoms, such as dyspnea, orthopnea, and gastric disturbance, were noted.

They were then placed on the drug Mictine and carefully instructed as to dose and manner of ingestion. The drug was obtainable at each visit only, and enough was given to last until the next scheduled visit. In this manner, it was possible to obtain a satisfactory rate of attendance. The dose used varied from 0.8 to 1.6 Gm., according to the response of the individual. It was altered as indicated by increased weight, signs of toxicity, and effective...

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mercurial therapy was reinstituted. A third patient, S.M., also on previous biweekly therapy, was adequately controlled on oral therapy of 1.2 Gm. for 4 months. At the end of that time he began gaining weight and showed an increase in edema. This patient had cor pulmonale of rather severe degree. Sixteen of the remaining 21 patients were adequately controlled, with complete suspension of their injections for varying periods. The longest such period was 5 months. There was no significant alteration in their weight curve, and no clinically detectable sign of increased fluid retention. They had all required weekly injections during the period of screening to control weight gain and symptoms of congestive heart failure. At differing time intervals, each began

diuresis as noted subjectively by the patient. Initially, one-half the group took Mictine on alternate days and the remainder on 3 consecutive days of each week. Within a few weeks it became evident that the latter was more desirable. A more effective diuretic action was obtained, and the control of weight was more easily accomplished. The patients were observed for 6 months. The results are summarized in table 1.

RESULTS AND CONCLUSIONS

Two of the 24 patients, C.G. and B.S., who had required mercurial injections biweekly, were not benefited at all. In a very short time they had to be given their usual injection. The drug was increased in both cases from 0.8 to 1.6 Gm., (the maximum tolerated dose for all our patients), without any effect on the inexorable weight gain observed until parenteral
to show a rise in weight and finally had to be given an injection again. The remaining 5 patients, all requiring at least 1 injection weekly prior to their inclusion in the study, are satisfactorily controlled to date. They are edema-free, with no increase in weight, and state that they feel as well as they did during the months of injection therapy. They are uniformly pleased at the possibility of foregoing the weekly injections.

It is too early to conclude that a satisfactory oral, nonmercurial diuretic has been obtained. In 16 patients an apparently refractory state developed that required a return to parenteral therapy, and the patients in severe heart failure were not benefited to any degree at all: these difficulties emphasize the need for a continued search for the ideal oral diuretic. Nevertheless, the significant number of patients who were improved and the number whose injections were spaced out over increased intervals made us believe that Mictine warrants a trial in patients who have moderate fluid retention and in those who require only intermittent mercurial diuretic therapy.

Repeated laboratory analyses did not disclose any abnormal alteration in blood chemistry. Therefore, it is reasonable to conclude that the drug is among those that should be considered in all cases where mercurials appear to be contraindicated.

The 16 patients who became refractory to Mictine have been placed on another pyrimidinedione derivative, and have shown a significant weight loss and reduction in edema. It is, however, too soon to determine the clinical value of this drug. It is planned to report on this group of patients when an adequate trial of at least 6 months have passed.

Toxic symptoms associated with Mictine were numerous at the outset of the study. There were many complaints of epigastric distress, nausea, and occasional epigastric pain. These appeared as the dose neared 1 Gm. daily. All these complaints ceased when the patients were instructed to take their pills with their meals. In those whose dose was raised progressively in order to achieve optimum control, a limit of 1.6 Gm. daily was reached, beyond which no further increase was tolerated.

The optimum dose was found to vary considerably. It always was between 0.6 and 1.2 Gm. and was best given in divided doses with meals for 3 days per week.

Summary

Thirty patients with fluid retention secondary to heart disease were studied in a clinical trial of the drug Mictine. Twenty-four, who participated in the trial for a period of at least 6 months, are reported. In 5 of these, completely satisfactory control was obtained without need for injections of mercurial diuretics. Sixteen received some relief for periods up to 5 months. In all these cases, injections of a mercurial diuretic were spaced out over longer intervals. One patient with severe cor pulmonale, requiring bieweekly injections prior to the study, was controlled for 4 months before further parenteral therapy was needed. Two who had severe congestive heart failure requiring biweekly injections of mercurials were not benefited at all. There was no significant alteration in blood chemistry values observed during the entire period of the trial. The drug must be taken during meals in order to avoid gastric irritation, which was the only sign of toxicity observed. The optimum dose varies for different patients. It was found to be between 0.8 and 1.2 Gm., given 3 days consecutively per week. A dose greater than 1.6 Gm. was not tolerated by any patient without symptoms of severe gastric irritation. The drug deserves trial in cases of moderate congestive failure and in all cases where mercurial diuretic therapy is contraindicated.

Summario in Interlingua

Trenta patientes con retentio de fluido, secundari a morbo cardiae, esseva studiate in un test clinic del droga Mictina. Vinti-quatro patientes participava in le test durante un periodo de al minus 6 menses. Le presente reporto es restringite a istes. In 5 de illes, un completaente satisfacente domination esseva obtenita sin ulle necessitate de injectiones de diureticos mercurial. Decesex obteneva un
certe alleviamento durante periodos de usque a 5 menses. In omne casos de iste gruppo, injectiones de un diuretico mercurial eseva administrate con plus longe intervallos. Un paciente con sever corde pulmonal requireva injectiones biseptimanal ante le periodo del studio. Sub tractamento a Mietina su condition eseva dominate durante 4 menses ante que le uso del therapia parenteral eseva de novo requirite. Duo patientes con sever congestive disfallimento cardiac—requirente injectiones biseptimanal de mercuriales—non beneficiava de Mietina del toto. Nulle significativa alteration de valores sanguino-chimic eseva observate durante le integre periodo del studio. Le drogo debe esser prendite con repastos pro evitar irritation gastric. Isto eseva le sol signo de toxicitate observate. Le dosage optimal varia ab un paciente al altere. Illo se trovava inter 0,8 e 1,2 g, administrate 3 dies consecutive per septimana. Doses supra 1,6 g non eseva tolerate per ulle paciente sin symptomas de sever irritation gastric. Le drogo merita un proba in casos de moderate disfallimento congestive e in omne casos de contraindication de therapia a diureticos mercurial.

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