Experience with Thiomerin, A New Mercurial Diuretic

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Thiomerin, a new mercurial diuretic, was given subcutaneously to 109 patients in whom fluid accumulations were present. Most patients suffered from congestive heart failure. It was used first under close supervision in hospitalized patients and later in ambulatory patients. In certain patients it was possible to compare the diuretic response to Thiomerin given subcutaneously with that to Mercuzanthin and/or Mercuhydrin given intramuscularly or intravenously. The untoward effects of these mercurial diuretics were compared with those caused by Thiomerin. The advantages of a subcutaneous mercurial diuretic are pointed out.

Since the introduction of Salyrgan by Bernheim in 1924, a continued search has been made for potent, more easily administered, less toxic mercurial diuretics. Salyrgan and Novasurol could be given only intravenously because of local tissue damage if any escaped from the vein. It was later observed that the inclusion of theophylline in the solution to be injected not only enhanced the diuretic effect of the mercurial radical, but also markedly diminished the deleterious tissue reaction which occurred if any of the drug escaped into the subcutaneous tissues. As a result, certain preparations incorporating this principle were made. It was found that these drugs could be given intramuscularly without tissue damage.

In the continued search for less toxic drugs in this category of diuretics, a new mercurial diuretic, Thiomerin, was recently introduced. It was found by early tests that it was an effective diuretic when given intravenously and intramuscularly, but, more important, that it could be given subcutaneously without local tissue damage and with satisfactory diuresis. Thiomerin differs from the mercurial diuretics which preceded it in that it is a mercaptide. Moreover it is not combined with a xanthine drug as are both Mercuzanthin* and Mercuhydrin.† It is the disodium salt of N-(gamma-carboxymethylmercaptopemercuri - beta-methoxy)-propyl camphoramic acid and has the following structure:

\[ C(CH_2)_2C(COONa)CH_2CH_2CHCONHCH_2CH_2(C)HgSCH_2COONa \]

Dissolved at a pH of 7.5, it contains approximately 0.039 Gm. of mercury per cubic centimeter, as do Mercuzanthin and Mercuhydrin.

Lehman, in a comparative study of the cardiac toxicity of the mercurial diuretics, found that the intravenous administration of Thiomerin to anesthetized cats caused no immediate changes in the electrocardiogram in doses up to 160 times the maximal tolerated dose of Mercuhydrin and up to 225 times that of Mercuzanthin. Taube, Lehman and King found that the intramuscular injections in rats of each of the three drugs, Thiomerin, Mercuhydrin and Mercuzanthin, caused an initial inflammatory reaction and exudate. Microscopic changes thought to be irreversible were present 96 hours following the injection of both Mercuhydrin and Mercuzanthin, but the exudate was completely reabsorbed in those animals receiving Thiomerin.

Grossman, Weston, Edelman and Leiter, in a preliminary report of the results of administration of approximately 200 subcutaneous injections of Thiomerin, found the diuretic effect to be similar to that following Mercuzanthin and Mercuhydrin. Herrmann, Chriß, Hejmanek and Sims present evidence that Thiomerin has the following advantages over the older organic mercurial diuretics: it is less toxic; it can be given subcutaneously and has a more even diuretic action. Recently Batterman, Unterman and DeGraff have reported observa-
tions on the use of Thiomerin which also indicate that it is an effective diuretic agent.

The effects of Thiomerin* have been observed on the pavilions and in the out-patient Cardiac Clinic of the New York Hospital in 109 patients during the last fourteen months.

METHODS

Patients who were selected for this study had evidence of accumulation of excess fluid in the tissues. Most of the patients were suffering from congestive heart failure. Fifty-two patients were treated in the pavilions of the New York Hospital. Most of them were at rest in bed. The salt in the food was limited to 1.0 to 3.0 Gm. daily. Fluid intake was restricted in certain patients to 1000 to 1800 cc. daily and in others it was not limited. Whenever possible the patient was weighed daily and the twenty-four-hour fluid intake and urine output were recorded. Thiomerin was substituted for Mercuzan-thin or Merehydron in patients who had been receiving these drugs in order to form the basis for comparisons. In others, Thiomerin was used as the initial diuretic and an occasional injection of Mereuzanthin or Merehydron was given to observe their effects by way of comparison. The dosage of Thiomerin varied from 0.25 cc. to 2.0 cc. The amount and frequency of administration were governed by the patient's requirements.

The drug was given subcutaneously in nonedematous areas to all patients but two. To one of these it was given intravenously because of the appearance of moderately tender local nodules at the site of the subcutaneous injections. To the other one it was given intravenously because of extreme emaciation. One patient was taught to give herself the injections subcutaneously. This practice has continued satisfactorily to the present.

Fifty-seven ambulatory patients were treated in the Cardiac Out-Patient Clinic of the New York Hospital. The regimen was similar to that followed for the pavilion patients except that measurement of the daily urinary output was not recorded. Weight records were kept, however.

OBSERVATIONS

Thiomerin was given to 109 patients, 52 being pavilion and 57 ambulatory patients. Twelve of the pavilion patients also received the drug in the Cardiac Clinic. Five of the 57 ambulatory patients are not included in the statistical analysis as they received single injections and follow-up data were not available.

There were no immediate untoward reactions following these single injections. Fifty-seven of the patients were males and 47 females. The ages ranged from 14 to 86 years.

Ninety-four patients presented evidence of congestive failure. The etiology of the heart disease was rheumatic fever in 26, arteriosclerosis in 26, hypertension in 12, both arteriosclerosis and hypertension in 21, constrictive pericarditis (postoperative) in 5, syphilis in 3, pulmonary fibrosis in one and a congenital anomaly in one. Nine other patients were treated because of evidence of excess fluid in the tissues. In 5 of these the diagnosis was cirrhosis of the liver, in 2 hepatitis, and in 2 carcinomatosis.

A total of 1,021 injections was given to the 104 patients. The dosage of 1.0 cc. was used in 366 injections and 2.0 cc. in 649. In the other six injections, intermediate amounts were given. The initial dose was usually 1.0 cc. Smaller doses than this were given when sensitivity to mercury was suspected. In one patient, 1.0 cc. proved to be too large and 0.5 cc. was given subsequently.

The frequency of injections is recorded on figure 1. Most patients received injections on a bi-weekly or weekly schedule. In 9 patients, daily injections were given, although this is not usually recommended. On the daily schedule, however, few received more than six injections.

* Thiomerin was supplied by Campbell Products Inc., New York, N. Y.
EXPERIENCE WITH THIOMERIN

One individual was given 2.0 cc. of the drug daily for sixteen days, without experiencing untoward effects. Excellent diuresis resulted in a weight loss of 9.0 Kg. The largest number of patients received from six to ten Thiomerin injections; 5 received more than thirty-one, and 2 more than fifty.

The diuretic effect of Thiomerin in a 78 year old man suffering from congestive failure is shown in figure 2. Dyspnea, orthopnea, pulmonary edema and massive anasarca were present. He was digitalized on admission and placed on a 3.0 Gm. salt diet. Nine injections of Thiomerin were given over a twenty-one-day period. Excellent diuresis resulted in a weight loss of 16.0 Kg. Because of the patient's difficulty in voiding, an indwelling catheter was maintained in place during the period of these observations. The collection and measurement of urinary output were therefore accurate.

The diuretic effect of Thiomerin was compared with that of Mercuzanthin in similar dosages in 54 patients and with that of Mercuhydrin in 22, regarding loss in weight or diuresis or both. In 5 patients the latter was possible. One significant difference between Thiomerin and the other two drugs was observed in 67 of these patients. Thiomerin resulted in a more even and more prolonged diuresis, which usually began twelve to eighteen hours after the injection and might continue for forty-eight hours. In 11 patients, Thiomerin was superior

**Fig. 2.**—Diuretic effect of thiomerin in patient T. N., suffering from congestive heart failure.
tivity reactions to these drugs. In one of these 3 patients a rash and fever followed on each occasion that Mercuhydrin was given. Mercuzanthin in 2.0 cc. amounts given intravenously had become relatively ineffectual. The patient suffered from severe congestive failure and massive anasarca was present. One cubic centimeter of Thiomerin was given subcutaneously on six occasions over a seven-day period. Diuresis was marked, resulting in a weight loss of 9.9 Kg. Five more injections over a ten-day period resulted in a further loss of 6.0 Kg. in weight with dramatic clinical improvement. Untoward reactions to Thiomerin have not appeared in this patient. Since then, she has received more than fifty injections in the Cardiac Clinic. The second patient developed an urticarial reaction to Mercuhydrin and the third, the same type of reaction to Mercuzanthin. Thiomerin has been effective as a diuretic in both of these patients without sensitivity reaction.

The diuretic effect of Thiomerin did not seem inferior to the effects of the other mercurial drug to which it was compared in any patient. In 22 patients an opportunity for comparison with the other mercurial drugs was not possible as only a few injections of Thiomerin were required to effect adequate diuresis, after which diuretics were no longer required.

Two patients received the drug intravenously subsequent to its use by the subcutaneous route. In them the total diuretic effect was approximately the same as by the subcutaneous route, although the onset of diuresis was more rapid and its duration less prolonged.

An estimate of the effect of Thiomerin on the body weight was possible in 89 patients. Loss of weight occurred in 47. The weight remained stable in 41 subjects. Only one patient in the whole series gained weight due to fluid accumulation while receiving Thiomerin in adequate dosage and frequency. This subject was a 44 year old alcoholic suffering from cirrhosis of the liver. Ascites was increasing. No better effect resulted from Mercuhydrin than from Thiomerin in similar amounts.

Eighty-six patients were on maintenance amounts of digitalis; 26 were also receiving ammonium chloride. In 7 patients when ammonium chloride was discontinued temporarily, slight but definite decreases in diuresis and gains in weight were recorded.

Reactions to Thiomerin

Temporary local pain or tenderness was the most common complaint. It occurred occasionally in 42 patients. The discomfort usually lasted from one minute to one hour and was described as varying from mild to moderate in intensity. In rare instances it was described as having a burning quality. Discomfort was accompanied in 4 patients by local ecchymosis which subsequently cleared entirely and did not prevent the continued use of the drug. In 6 other patients, moderately tender nodules appeared occasionally at the sites of injection. These were slowly reabsorbed over a seven- to ten-day period. In one patient they appeared more frequently and were more persistent. For this reason the drug was subsequently given by the intravenous route without untoward reaction. These reactions have not occurred with later batches of the drug.

Cramps in the calves of the legs were recorded in 3 patients when the diuresis was perhaps too large and too rapid. When either the dose of the drug or the frequency of injections was reduced these symptoms did not occur.

A superficial slough occurred in the skin in one patient. This untoward result followed the ninth injection the patient had received. It was given superficially and quite likely, in part, intradermally. The use of the drug was subsequently continued in this patient, with precautions taken for subcutaneous administration, and the area of superficial slough healed without further untoward reactions. This reaction was attributed to the drug being given too superficially.

Reactions were not observed in 58 patients.

Discussion

Our observations indicate that Thiomerin is as effective a diuretic agent as Mercuzanthin and Mercuhydrin. In a small number of patients in whom comparison was possible it appeared to be more effective than the latter two drugs so that smaller doses and less frequent injections
could be given. In no instance was it found to be inferior.

In addition, it has a major advantage over these two drugs in that it can be given subcutaneously. Thus, as experience with the drug accumulates, patients may be taught to administer this drug to themselves, just as they do with insulin. One patient of this group and two others not included because of incomplete data have been injecting the drug subcutaneously to themselves safely. A study is being set up with the idea of exploring the possibility of patients administering the drug themselves.

With few exceptions, patients, who have been receiving mercurial diuretics intramuscularly or intravenously, expressed preference for the subcutaneous route. In some patients much persuasion was required before they would submit to intermittent injections of the older mercurial drugs in order to obtain comparative observations.

Another advantage appreciated by most patients was the more even and persistent diuretic effect, sometimes lasting for several days. Many of the patients attending the afternoon Cardiac Clinic had become accustomed to little sleep on the night following injections because of profuse diuresis. When Thiomerin was substituted, certain patients remarked that less sleep was lost. With the use of this drug, also, complaints of cramps in the calves of the legs have become rare.

For the patient who was sensitive to Mercuhydrin and relatively refractory to Mercuzanthin, Thiomerin appeared to be life-saving. Diuresis resulted in a weight loss of 16.5 Kg. over a seventeen-day period. In 2 other patients who developed urticaria following the other mercurial diuretics, sensitivity to Thiomerin did not occur. Ammonium chloride appeared to enhance the action of Thiomerin.

There were no serious immediate or delayed toxic reactions to Thiomerin. Pain, palpitation, collapse, dyspnea, cardiac arrhythmias and evidences of renal damage were not observed. To one patient, injections of 2.0 cc. amounts of the drug were administered on sixteen consecutive days without toxic manifestations. This method of administration is, however, not recommended because of the danger of a cumulative effect of mercury and the untoward effects of extreme dehydration.

There is one drawback which the manufacturers are improving with each new batch of the drug. It cannot be made up in solution before distribution by the manufacturer because it is unstable. The latest batches which have been supplied to us may be kept without deterioration up to four to six weeks after being dissolved, provided they are kept in an icebox.

The results in these patients lead us to conclude that Thiomerin is a valuable contribution to the list of mercurial diuretic drugs. It appears to be as effective as the older ones and has the advantage that it can be given subcutaneously. Moreover, from animal experiments, it appears less toxic than these, but care must be exercised that it is given subcutaneously and not in the skin. At the present time it appears to be the diuretic of first choice.*

**SUMMARY**

Thiomerin is a new mercurial diuretic which may be given subcutaneously as well as intramuscularly and intravenously. One hundred and nine patients with evidence of excess fluid in the tissues, most of them suffering from congestive heart failure, were given a total of 1,021 injections of the drug. From this experience we feel the drug is an effective diuretic agent. The local discomfort from the injection when it is given subcutaneously is minimal. In a few patients a subcutaneous nodule appeared at the site of injection in early preparations of the drug, but this reaction has not followed the later preparations of the diuretic. Care must be exercised that the drug is given subcutaneously and not intradermally.

Thiomerin was compared to Mercuhydrin or Mercuzanthin or both in 84 patients. In 67 of this group the total diuretic effect was similar in all three drugs. A more prolonged and more even diuresis, however, followed the use of Thiomerin. In 11 patients the total diuretic effect of Thiomerin was superior to these and

* Since this paper was accepted for publication, 2315 additional subcutaneous injections of Thiomerin have been given over an eight month period. This further experience has increased our confidence in this drug as a diuretic agent.
the dose and frequency of injections could therefore be decreased. In 3 patients it was substituted because of sensitivity to Mercuzanthin or Mercuhydrin and was tolerated without sensitivity reaction. No serious toxic effects occurred. Thiomerin appears to us to be the drug of first choice at the present time for most patients requiring mercurial diuretics.

REFERENCES


Experience with Thiomerin, A New Mercurial Diuretic
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