Penicillamine-Induced Cupriuria in Normal Subjects and in Patients with Active Liver Disease (36973)

R. E. LYNCH, G. R. LEE, AND G. E. CARTWRIGHT

Department of Medicine, University of Utah, College of Medicine, Salt Lake City, Utah 84112

Wilson's disease may be difficult to diagnose in its early stages if unaccompanied by Kayser-Fleischer rings, neurologic disease and hypoceruloplasminemia (1). In the active hepatic stage, the disorder may be indistinguishable clinically from chronic active liver disease (2); the serum copper and ceruloplasmin may not be decreased; and the patient may be too ill to permit hepatic biopsy. It would be helpful in such situations if a diagnostic test to detect copper-overload were available.

The cupriuric effect of D-penicillamine in Wilson's disease is well recognized (3–5) and the increased excretion of copper in the urine following the oral administration of penicillamine has been used as evidence for the diagnosis of Wilson's disease (6, 7). However, few studies have been reported on the excretion of copper in the urine following the administration of penicillamine to normal human subjects or to patients with active liver disease. The purpose of this paper is to provide such data.

Methods. Twenty-four hour urine collections were obtained for 2 to 4 days preceding penicillamine administration. D-Penicillamine (Cupramine, Merck, Sharp and Dohme) (0.5 g) was given orally three times daily and the urine was collected for 2 to 5 days. All glassware used for the collection of urine was cleaned to avoid copper contamination. Urine copper, serum copper and ceruloplasmin were measured by methods published previously (1).

The excretion of copper was measured in four normal healthy subjects and the test was repeated in one of the subjects.

Patients with chronic active liver disease were selected for the study. A liver biopsy was performed on all six patients and active necrosis, inflammation and varying degrees of fibrosis were observed in all specimens. The diagnosis was chronic active hepatitis (chronic aggressive hepatitis) in two (K.M., F.S.), cryptogenic cirrhosis in two (J.B., C.M.), alcoholic hepatitis in one (P.W.) and toxic hepatitis in the sixth (M.B.). None of the patients had any of the stigmata of Wilson's disease and the serum copper and ceruloplasmin concentrations were normal or increased (Table I).

Results. Before penicillamine the normal subjects excreted 16 to 40 μg of copper in the urine/day (mean, 24 μg/day). After penicillamine the excretion increased to 832 to 1325 μg/day (mean maximal value of 1082 μg/day) (Fig. 1). The patients with liver disease excreted 17 to 107 μg/day (mean, 50 μg/day) before penicillamine and this increased to 663 to 1390 μg/day (mean maximal value of 1022 μg/day) after penicillamine.

Discussion. Walshe (3) measured the urinary excretion of copper in two normal subjects after administration of 0.9 of D-penicillamine and obtained values of 630 and 720 μg/day. Tu and Blackwell (6) gave 1 g of DL-penicillamine to 26 normal subjects and obtained a mean value of 640 μg/day with a range of 270 to 1160 μg/day. Our mean value 1325 μg/day is greater than the values of the above workers because of the larger daily dose (1.5 g of the D-isomer) which we administered.

The excretion of copper in the urine of the patients with chronic active liver disease was not significantly different from the normal

[1] This work was supported by Research Grant (AM-04489), Graduate Training Grant (AM-5098), and Clinical Research Center Grant (FR-00064), National Institutes of Health.

TABLE I. Data on the Patients With Liver Disease.

Patient	Age (yr)	Sex	Serum copper (μg/100 ml)	Ceruloplasmin (mg/100 ml)	SGOT[a]	Serum bilirubin (mg/100 ml)
Normal subjects[b]			81–147	25–43	15–48	0.1–0.8
K.M.	17	F	142	49	1570	5.2
F.S.	18	M	182	43	1590	8.0
J.B.	18	M	160	49	83	0.6
P.W.	21	F	183	52	440	1.3
M.B.	44	F	134	36	87	0.4
C.M.	36	M	96	32	85	6.4

[a] SGOT, serum glutamic-oxaloacetic transaminase (mU/ml).
[b] Values refer to 95% limits.

subjects after penicillamine administration (Fig. 1).

Patients with Wilson's disease given 0.9 to 1.5 g of D-penicillamine excrete 1800 to 7000 μg of copper/day in the urine during the first days of therapy (3–6). The greatest value which we obtained in the normal subjects or in the patients with chronic active liver disease was 1390 μg/day. Therefore, the urinary copper excretion test may be of value in differentiating patients with Wilson's disease from patients with chronic active liver disease.

It should be pointed out that our study did not include patients with primary biliary cirrhosis. Such patients may have a greatly increased concentration of copper in the liver (8) and it is entirely possible that penicillamine may induce a greater increase in urinary copper in such patients than in patients with nonobstructive liver disease. However, primary biliary cirrhosis can be easily differentiated from the active hepatic form of Wilson's disease by other means.

Summary. The urinary excretion of copper was measured in four normal subjects and in six patients with chronic active liver disease following the oral administration of 1.5 g of D-penicillamine/day. All individuals excreted a maximum of 663 to 1390 μg of copper/day

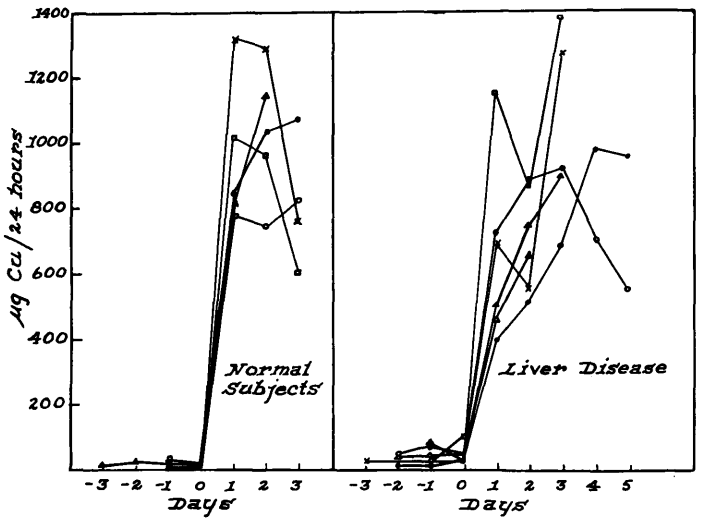

FIG. 1. Urinary excretion of copper in normal subjects and in patients with chronic active liver disease before and after the oral administration of 1.5 g of D-penicillamine/day beginning at Day 0.

and there was no difference between the two groups. Since patients with Wilson's disease excrete more than 1400 μg of copper in the urine/day following penicillamine therapy, this test may be of value in differentiating patients with Wilson's disease from patients with chronic active liver disease.

We are indebted to Miss Jacqueline Thomas and Mrs. Alice Tustison for technical assistance.

1. Deiss, A., Lynch, R. E., Lee, G. R., and Cartwright, G. E., Ann. Intern. Med. **75**, 57 (1971).

2. Sternlieb, I., and Scheinberg, I. H., Ann. Intern. Med. **76**, 59 (1972).

3. Walshe, J. M., Amer. J. Med. **21**, 487 (1956).

4. Walshe, J. M., Lancet **1**, 188 (1960).

5. Scheinberg, I. H., and Sternlieb, I., Amer. J. Med. **29**, 316 (1960).

6. Tu, J-B., and Blackwell, R. Q., Metabolism **16**, 507 (1967).

7. DuBois, R. S., Rodgerson, D. O., Martineau, G., Schroter, G., Giles, G., Lilly, J., Halgrimson, C. G., and Starzl, T. E., Lancet **1**, 505 (1971).

8. Worwood, M., Taylor, D. M., and Hunt, A. H., Brit. Med. J. **3**, 344 (1968).

Received July 17, 1972. P.S.E.B.M., 1973, Vol. 142.