Is D-Penicillamine Useful in Fulminat Wilson's Disease?

Wilson's disease with severe hepatic insufficiency: Beneficial effects of early administration of D-penicillamine. *Durand F, Bernuau J, Giostra E, Mentha G, Shouval D, Degott C, et al.* Gut 2001;48:849-852. (Reprinted with permission from the BMJ Publishing Group.)

Abstract

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Comments

Liver disease in Wilson's disease (WD) ranges from a mild elevation of serum aminotransferase levels in asymptomatic individuals to fulminant disease and cirrhosis. Sometimes the initial presentation is fulminant hepatic failure characterized by hepatic encephalopathy, hemolytic anemia, progressive jaundice, ascites, and renal failure.[1]

The key therapeutic strategy is to reduce the amount of copper in the liver and other tissues by administering copper-chelating agents. There are several effective chelating agents, such as D-penicillamine, trientine, and zinc salts. D-Penicillamine and trientine are the copper-chelating agents most commonly used. D-Penicillamine chelates copper to form stable soluble complexes, which are excreted readily by the kidneys. Copper is chelated by the combination of two molecules of D-penicillamine with one atom of the metal. The drug is believed to be metabolized in the liver and excreted in urine and feces, principally as inactive disulfides. Approximately 50% of a dose of penicillamine is excreted in urine, approximately 20% is excreted in feces, and approximately 30% is unaccounted for after 24 hours.[2]

Patients presenting with fulminant WD either as the first symptom or because they discontinue chelating therapy should be listed as status I for emergency liver transplantation (LT).[3] Although D-penicillamine can be prescribed in this clinical setting, it is considered ineffective. The overall 1-year survival rate for patients with WD and end-stage liver disease who undergo LT is approximately 85%, and it is less in patients with fulminant hepatic failure (67%).[4,5] Other copper-lowering modalities have been used, but the goal has been to reach LT.[6,7]

Durand et al studied a group of 17 consecutive patients with severe hepatic insufficiency caused by WD as the first symptom of disease from 1969 to 1999. They compare their experience before 1979 (period 1; patients were not administered D-penicillamine) with 1979 to 1999 (period 2; D-penicillamine routinely was administered). Only 2 of the 17 patients presented with hepatic encephalopathy and could be considered fulminant WD. These 2 patients were not treated with D-penicillamine and underwent urgent LT. Another patient developed encephalopathy despite D-penicillamine treatment and also underwent LT. During the first period, 4 patients were not administered chelating agents, and they all developed encephalopathy and died. In the second period, D-penicillamine was administered to 11 patients with WD and severe hepatic insufficiency without encephalopathy. Only 1 patient in this group developed hepatic encephalopathy 36 days after admission and was listed for emergency LT. The remaining 10 patients in this group survived without the need for LT, with a mean follow-up of 6 years.

Although results are encouraging, several aspects deserve further discussion. Two patients with renal failure on admission (serum creatinine levels, 2.9 and 2.3 mg/dL) were administered D-penicillamine. It is commonly known that patients with a glomerular filtration rate less than 50% should not be administered D-penicillamine.[8] Another patient developed renal failure dur-

ing treatment with D-penicillamine and also developed hepatic encephalopathy; this was the only patient in the second group who underwent LT. Not much information is provided to learn how the investigators successfully circumvented an old clinical dogma.

It is well known that D-penicillamine has at least 20% of early side effects, manifested by fever, rash, lymphadenopathy, leukopenia, thrombocytopenia, or some combination of these. One surprising result is that no serious adverse effects were seen in this group of patients.

In summary, Durand et al found that D-penicillamine was effective in 10 patients who presented with decompensated hepatic disease and did not have hepatic encephalopathy. This approach is not much different from conventional practice and reinforces that chelating therapy can provide a stabilizing effect in patients with WD with decompensated liver disease without hepatic encephalopathy. The investigators also found that this beneficial effect is durable, and patients may survive without the need for urgent LT. However, these patients need to be seen regularly by a liver transplant team because they may develop such complications associated with cirrhosis as bleeding varices, ascites, hepatic encephalopathy, and, to a lesser extent, hepatocellular carcinoma.[9,10]

Jorge Rakela, MD
Hugo Vargas, MD
Juan Arenas, MD
Mayo Clinic Scottsdale
Scottsdale, AZ

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