D-PENICILLAMINE

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D-penicillamine is a derivative of the penicillin molecule and was first identified in 1953 in the urine of patients with chronic liver diseases who were receiving penicillin for treatment of intercurrent infections(1). Two years later Walshe(2) demonstrated its effectiveness as a copper chelating agent and introduced it in the treatment of Wilson's disease. While it has been proven to be effective in management of heavy metal poisoning, cystinuria, Wilson's disease and rheumatoid arthritis, its use in conditions like primary biliary cirrhosis, chronic-active hepatitis and scleroderma is still not well-established(1,3-6). Inspite of its many uses, the exact mechanisms of its action are only partially understood.

D-penicillamine has not only revolutionized the treatment of Indian Childhood Cirrhosis (ICC) but has also helped in improving our understanding of the disease(7). Hitherto considered a uniformly fatal condition, the outlook of children with ICC has now improved considerably and in early stages, the drug may be curative.

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Chemistry

Penicillamine is a sulfhydryl amino-acid and chemically is β-β-dimethyl cysteine. It is prepared by the hydrolytic degradation of penicillin. It can be manufactured synthetically. It has no antibacterial property.

D, DL & L forms: Though all the three forms of penicillamine have chelating activity, it is the 'd' isomer which is used clinically. The others have a significant antipyridoxine effect secondary to formation of a thiazolidone between penicillamine and pyridoxal phosphate. This may, at times, result in optic neuritis(8,9). Anti-pyridoxine effect of the 'd' isomer does not appear to be clinically significant, but, supplements are nevertheless, recommended specially in growing children and children with borderline nutritional status.

Pharmacokinetics

D-penicillamine is well absorbed from the gastrointestinal tract and reaches peak concentration in blood 1-2 hours after oral administration. In animal studies using radioactive penicillamine, it was found that the drug accumulates in collagen containing tissues (*e.g.,* skin, tendons)(9). Hepatic biotransformation is responsible for most of the degradation of penicillamine. It is metabolized to the oxidized form and excreted in urine as either the internal

disulfide (pen-pen) or the mixed disulfide (pen-cysteine). Metabolites of the drug are found in both urine and feces. Very little proportion of the drug is excreted unchanged. Though excretion is rapid, traces of penicillamine are found in the plasma even after 48 hours, due, primarily to protein binding with albumin, α-globulin and ceruloplasmin.

Though, *in vitro*, both penicillamine and cysteine form stable metal chelates, *in vivo*, only penicillamine is effective in promoting excretion of metals. This is due to the degradation of cysteine by desulfhydrase; penicillamine, however, is resistant to such action.

Mechanisms of Action

A. *Wilson's Disease*

Penicillamine chelates copper and induces a cupriuresis, thereby leading to a decrease in stored copper. Clinical improvement depends on the stage of the disease at which therapy was started. Apart from copper it also chelates zinc, lead and mercury.

B. *Indian Childhood Cirrhosis (ICC)*

Penicillamine induces a cupriuresis in ICC, the magnitude of which is significantly more than that in other chronic liver diseases. Clinical improvement of ICC patients on long-term therapy with d-penicillamine is associated with progressive reduction in hepatic copper concentration and associated improvement in liver histology(7,10), copper chelation, therefore, is proposed to be the main mechanism of action. However, other action of the drug may also play a role in this disease. For instance, penicillamine as a sulfhydryl donor may help in the regeneration of reduced glutathione, which may have a cytoprotective effect(10). Pencillamine is known to interfere with collagen synthesis and thus may help in reduction of the aggressive pericellular fibrosis so characteristic of this disease(11). The immunomodulating effect of penicillamine may also be important because it leads to a fall in the circulating immune complex level, known to be raised in ICC(12). Lastly, the copper-penicillamine chelate is known to have an anti-inflammatory effect by the involvement of superoxide dismutase–this may be beneficial in ICC(13).

C. *Rheumatoid Arthritis*

The mechanism of action of penicillamine in rheumatoid arthritis remains uncertain. Clinical improvement may be due to its anti-inflammatory and immunomodulatory effects(5,14,15). Penicillamine is believed to interfere with RNA synthesis and suppresses human helper 'T' cells(16). Suppression of the disease may result from the decrease in concentration of IgM rheumatoid factor(15).

D. *Cystinuria*

The rationale for the use of penicillamine in cystinuria is that it forms a disulfide compound through the SH-SS interchange between penicillamine and cysteine(17). As this disulfide is considerably more soluble than cystine alone there is a prompt decrease in the size and ultimate dissolution of the cystine calculi.

E. *Scleroderma*

Penicillamine is known to interfere with cross linking of collagen. In collagen,

tropocollagen units are bound by aldehyde covalent linkages. Penicillamine interferes with the aldehyde residue and blocks development of stable covalent bonds, thereby resulting in increased solubility and fragility of the collagen(6,18). In fact, it is this property of penicillamine which has been exploited in chronic active hepatitis to prevent development of cirrhosis(19).

Uses of D-Penicillamine

A. *Wilson's Disease*

Diagnostic: The cupriuresis test has been used as a non-invasive diagnostic aid specially in early stages of the disease when urine copper excretion may be normal. On administration of 500 mg d-penicillamine orally, a urinary copper excretion of greater than 500-700 mcg/6 hours is suggestive of Wilson's disease while values less than 300 mcg/6 hours would be seen in controls(20,21).

Therapeutic: The most well-established use of d-penicillamine is in Wilson's disease. Response to therapy occurs after a latent period, the duration of which depends on the size of the abnormal copper pool and stage of the disease at which treatment is started. Improvement in biochemical parameters precedes clinical improvement. Features which respond well to therapy include tremors, dystonia, rigidity, K-F ring and early cirrhotic changes. On the other hand, gross psychiatric manifestations, dysarthrias and chronic active hepatitis, if present, are generally resistant to therapy(22). Treatment is life-long and periodic monitoring (serial liver function tests, handwriting records, clinical photographs of K-F ring on slit-limp examination) is essential.

B. *ICC*

Diagnostic: Walia *et al.*(23) measured urinary copper excretion before and during d-penicillamine administration (25 mg/kg/day in 2 divided doses orally for 3 days) in 15 patients with clinical and histological diagnosis of ICC; 13 patients with clinical diagnosis of ICC and 8 as controls. More than two-fold increase in urinary copper was observed in 14 of 15 patients with biopsy proven ICC, 9/13 in non-biopsy ICC and 0/8 in controls. The authors concluded, that a cut-off level of two-fold increase in urinary copper following penicillamine may be a useful noninvasive test in the diagnosis of ICC.

To obviate the need for 24 hours urine collections, Bhave *et al.*(10) have used the copper-creatinine ratio in random urine samples. Urine was collected from 57 children with ICC and 21 children with other hepatic disorders (6-chronic active hepatitis, 6-chronic persistent hepatitis, 1-Wilson's disease, 1-cryptogenic cirrhosis). In advanced ICC, urine copper concentration was higher (416-103448 mg/g creatinine). In early ICC (8 cases) urine copper concentration was modestly raised (1188-9470 mg/g creatinine), but rose to high values (2222-42,819 mg/g creatinine) after a single dose of d-penicillamine (20 mg/kg). A post-penicillamine urinary copper-creatinine ratio of 10,000 mg/g supports a diagnosis of ICC (in 7/8 cases). Other disorders associated with raised hepatic copper showed only a modest post-penicillamine cupriuresis.

Therapeutic: The most recent, and perhaps the most controversial, use of d-penicillamine is in ICC. Penicillamine was first tried in ICC in 1980 and since then it has been used by many workers(7,24-26).

Tanner *et al*, conducted a double-blind

TABLE I—*Side-Effects of D-Penicillamine*

Dermatologic	*Renal*
Early onset urticaria	Proteinuria (33%)
Late onset papular rash	Membranous glomerulonephritis
Pemphigus	Mesangioproliferative glomerulonephritis
SLE like rash	Good Pasture's syndrome
Epidermolysis bullosa	
Elastosis serpiginosa	
Hematologic	*Gastrointestinal*
Neutropenia	Hypogeusia (may be ameliorated by zinc administration)
Thrombocytopenia	Oral ulcers
Hemolytic anemia	Reactivation of peptic ulcer
Miscellaneous	
SLE	Hepatotoxicity
Myasthenia gravis	Dermatomyositis
Cholestatic jaundice	Diffuse alveolitis

TABLE II—*Points to Remember During Therapy with D-Penicillamine*

1. Baseline hemogram, urine examination. and liver function tests to be done before initiation of therapy.
2. In ICC and Wilson's disease ensure that
   (*a*) Copper/brass vessels are not being used for boiling and/or storing milk.
   (*b*) Foods rich in copper (*e.g.*, liver, shellfish, nuts, chocolates) should be avoided.
   (*c*) If copper content of drinking water is more than 0.1 mg/L, it should be demineralized.
3. Prophylactic pyridoxine should be given to prevent optic neuritis.
4. Penicillamine should be avoided in patients with penicillin allergy.
5. Penicillamine needs to be discontinued (? temporarily) if there is
   (a) Leucopenia, thrombocytopenia
   (*b*) Skin rash
   (*c*) Proteinuria
   (*d*) Myasthenia gravis
   (*e*) SLE

controlled trial in 30 children with early ICC (*i.e.,* before development of ascites or edema)(7). There were three treatment groups which were given either penicillamine, or penicillamine plus prednisolone, or a placebo. The dose of penicillamine was 20 mg/kg/day and of prednisolone 2 mg/kg/day for 4 weeks and thereafter 5 mg/day. Nine of the 10 untreated children died within 181 days (median 58 days). On the other hand, 5 children treated with penicillamine plus prednisolone survived 489-1460 days from the start of treatment. Life table analysis showed a significantly improved survival in both treatment groups compared with the group taking the placebo ($p \leq 0.05$). No difference in survival existed between the 2 treatment groups. When these 2 groups were pooled the difference in survival between treated children (n = 20) and the group taking placebo (n = 10) was highly significant ($p < 0.005$).

The clinical improvement is matched by a sequential decrease in hepatic copper concentration and a simultaneous improvement in the histopathologic picture. Therapy is generally continued till the histology, returns to normal and this may take 1-2½ yrs(7,26). In some patients with advanced ICC, however, the results are not that gratifying though it is possible that use of higher doses of penicillamine (*i.e.,* 40-50 mg/kg/day) in such cases may improve the results(25).

C. *Rheumatoid Arthritis*

Though penicillamine is effective in treatment of active rheumatoid arthritis in adults, its role in juvenile rheumatoid arthritis is less well-defined. However, it may have to be used in those children who require a disease modifying anti-rheumatic drug(28,29). Treatment for a few weeks is generally sufficient.

D. *Heavy Metal Poisoning*

Penicillamine is an effective chelator of lead, mercury, zinc and copper and promotes excretion of these metals in the urine(3).

Side-Effects of D-Penicillamine

The side-effects of d-penicillamine (*Table I*) are numerous(30-33). In one study of adult rheumatoid arthritis patients, it was found that 62% of the cases had toxic reactions, of which 36% required discontinuation of therapy. However, it appears that patients having Wilson's disease, as also those having ICC, tolerate the drug remarkably well(10). In the series reported by Tanner and Pandit, it was found, that though mild proteinuria was common at presentation, this did not increase with treatment and in no child did a rash or marrow suppression necessitate stoppage of the drug(6). Pregnancy, history of previous penicillamine induced agranulocytosis or aplastic anemia, and presence of renal insufficiency are considered absolute contraindications to the use of d-penicillamine.

Table II summarizes the points to remember during therapy with d-penicillamine.

REFERENCES

1. Klaasen CD. Heavy metals and heavy metal antagonists. *In:* The pharmacological Basis of Therapeutics, 7th edn. Eds Gilman AG, Goodman LS, Rall TW, Murad F. New York, Macmillan Publishing Company, 1985, pp 1605-1627.

2. Walshe JM. Penicillamine: A new oral therapy for Wilson's disease. Am J Med 1956, 21: 487-495.

3. Boulding JE, Baker RA. The treatment of metal poisoning with penicillamine. Lancet 1957, 2: 985.

4. Perrett D. The metabolism and pharmacology of d-penicillamine in man. J Rheumatol (Suppl) 1981, 8: 51-55.

5. Epstein O, DeVilliers D, Jain S, *et al.* Reduction of immune complexes and immunoglobulin induced by d-penicillamine in primary biliary cirrhosis. N Engl J Med 1979, 300: 274-278.

6. Moynahan EJ. Morphea treated with low dose penicillamine. Proc Roy Soc Med 1974, 66: 1083-1084.

7. Tanner MS, Bhave SA, Pradhan AM, Pandit AN. Clinical trials of penicillamine in Indian Childhood Cirrhosis. Arch Dis Child 1987, 62: 1118-1124.

8. Crossland J. Anti-inflammatory drugs. *In:* Lewis's Pharmacology, 5th Edn. Ed Crossland J. London, Churchill Livingstone, 1980, pp 455-456.

9. Jaffe IA. D-penicillamine. *In:* Textbook of Rheumatology, 2nd edn. Eds Kelly WN, Harris ED, Ruddy S, Sledge CB. Philadelphia, WB Saunders Company, 1985, pp 809-815.

10. Bhave S, Pandit A. D-penicillamine in the therapy of Indian Childhood Cirrhosis. Indian J Pediatr 1987, 54: 587-590.

11. Nimni ME, Bavetta LA. Collagen defect induced by penicillamine. Science 1965, 150: 905-907.

12. Lipsky PE, Ziff M. The effects of D-penicillamine on nitrogen induced human lymphocyte proliferation: synergistic inhibition by D-penicillamine and copper salts. J Immunol 1978, 120: 1006-1013.

13. Roberts NA, Robinson PA. Copper chelates of anti-rheumatic and anti-inflammatory agents: their superoxide-dismutase like activity and stability. Br J Rheumatol 1985, 24: 128-136.

14. Bluestone R, Goldberg LS. Effects of D-penicillamine on serum immunoglobulins and rheumatoid factor. Ann Rheum Dis 1973, 32: 50-53.

15. Wernick R, Merryman P, Jaffe I, Ziff M. IgG and IgM rheumatoid factors in rheumatoid arthritis. Arthritis Rheum 1983, 26: 593-598.

16. Lipsky PE, Ziff M. Inhibition of human helper T cell function *in vitro* by D-penicillamine and copper sulfate. J Clin Invest 1980, 65: 1069-1076.

17. Crawhall JC, Scowen EF, Watts RWE. Effects of penicillamine on cystinuria. Br Med J 1963, 1: 588.

18. Deshmukh K, Nimni ME. A defect in the intra-molecular and intermolecular cross linkages of collagen caused by D-penicillamine. J Biol Chem 1969, 244: 1787-1795.

19. Stern RB, Wilkinson SP, Howorth PJN, Williams R. Controlled trial of synthetic D-penicillamine in maintenance therapy for chronic active hepatitis. Gut 1977, 18: 19.

20. Silverman A, Roy CC. Chronic liver diseases. *In:* Pediatric Clinical Gastroenterology, 3rd edn. New York, The CV Mosby Company, 1987, pp 700-701.

21. Sass-Kortsak A, Bearn AG. Hereditary disorders of copper metabolism. *In:* The Metabolic Basis of Inherited Disease. Eds Stanbury JB, Wyngaarden JB, Frederickson DS. New York, McGraw Hill Book Company, 1978, pp 1098-1126.

22. Walshe JM. Wilson's Disease. *In:* Handbook of Clinical Neurology, Vol 27. Eds Vinken PJ, Bruyn GW, Klawans HL. Oxford North Holland Publishing Company, 1976, pp 379-414.

23. Walia BNS, Dilawari JB, Bajwa RPS, Singh S, Nath R. Copper excretion test in

Indian Childhood Cirrhosis. Hepatology 1988, 8: 1458.

24. Tomar BS, Saxena S, Prakash P. D-penicillamine in treatment of Indian Childhood Cirrhosis—a preliminary report. Indian J Pediatr 1983, 50: 613-618.
25. Kalra V. Dietary copper and ICC. Indian Pediatr 1986, 23: 399-409.
26. Walia BNS, Singh S. D-penicillamine in treatment of Indian Childhood Cirrhosis. (under publication).
27. Pandit AN. Personal communication.
28. Brewer EJ, Giannini EH, Kuzmina N, Alekseev L. Penicillamine and hydroxychloroquin in the treatment of severe juvenile rheumatoid arthritis. Results of USA–USSR double blind placebo controlled trial. N Engl J Med 1986, 314: 1269-1276.
29. Giannini HE, Brewer EJ. Juvenile rheumatoid arthritis: Principles of management. World Pediatr Child Care 1987, 3: 227-244.
30. Greer KE, Askew FC, Richardson DR. Skin lesions induced by penicillamine. Arch Dermatol 1976, 112: 1267-1269.
31. Rehan A, Johnson K. IgM nephropathy associated with penicillamine. Am J Nephrol 1986, 6: 71-74.
32. Vincent A, Newsom Davis J, Martin V. Anti-Ach receptor antibodies in D-penicillamine associated Myasthenia gravis. Lancet 1978, 1: 1254-1257.
33. Henkin RI, Keiser HR, Jaffe IA, Sternlieb I, Scheinberg IH. Decreased taste sensitivity after D-penicillamine reversed by copper administration. Lancet 1967, 2: 1268-1271.

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