Do Trace Elements, Magnesium and Anti-Oxidants Protect Against d-Penicillamine Toxicity?

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ABSTRACT

d-Penicillamine is a drug that is the treatment of choice in 2 uncommon metabolic diseases: Wilson's disease and cystinuria. It is effective in heavy metal poisoning and, when tolerated, has produced marked improvement in patients with auto-immune diseases such as rheumatoid arthritis and scleroderma. However, its high incidence of adverse reactions in patients with inappropriate immunologic responses has limited the use of effective doses in patients with rheumatoid arthritis and scleroderma; the use of low doses (250-750 mg/day) is being tried in the effort to reduce side effects. Trials of full-dosage (2 g/day) d-penicillamine plus vitamin B_6 and zinc (removed or inactivated by this agent), high doses of anti-oxidant vitamins and magnesium have produced improvement with minimal adverse reactions in patients with auto-immune diseases.

INTRODUCTION

Since Walshe's pioneering work with d-penicillamine in Wilson's disease, which was based on its Cu chelating activity and lack of acute toxicity with high doses in rodents (64), this agent's metal chelating properties were fairly safely applied to treatment of Wilson's disease and heavy metal toxicity (14) and its formation of soluble mixed disulfides of cystine to the treatment of cystinuria (7). Until its efficacy was demonstrated in pilot and controlled studies in such auto-immune diseases as rheumatoid arthritis, vasculitis and lung disease, and in scleroderma (5, 9, 15, 17, 20-24, 26, 27, 29, 38, 43, 44), it was considered a relatively non-toxic agent. Acute reactions were encountered, but those generally subsided fairly quickly; other adverse reactions were dose and time related (60). Serious side effects of d-penicillamine include immune reactions that have been reported in a third of rheumatoid arthritis patients (8, 10, 16, 18, 25, 30, 50, 51, 58, 60, 63).

Favorable results have been attained without side effects in a pilot study of the treatment of Laennec's cirrhosis with d-penicillamine (55)--a chelating agent which frees endogenous sulfhydryl [SH] groups and provides additional non-metabolized free SH-groups (64)--when it was used in conjunction with nutrients which it inactivates (vitamin B_6) (28, 33) or removes (zinc) (31), SH-protecting vitamins (E, B_1, B_{12}, C) and Mg when a deficit was demonstrable. Thus the same combination of nutrients was used on extension of therapeutic trials of d-penicillamine in additional chronic diseases with auto-immune components: multiple sclerosis, rheumatoid arthritis and dysproteinemias or reticuloses. In contrast with the one-third incidence of intolerable side effects reported in the literature, which has led to trial of very low doses of d-penicillamine in rheumatoid

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arthritis (10; I. A. Jaffe, personal communication), we have encountered only 3 urinary abnormalities (only one of which is unexplained by extraneous conditions) among our almost 50 patients, 18 of whom have received 2 g of d-penicillamine/day or more for 16-40 mo.

MATERIALS AND METHODS

Patients with chronic diseases (progressive Laennec's cirrhosis, multiple sclerosis and miscellaneous reticuloses) have been pre-treated for at least one mo with vitamins divided into 3 daily doses with meals: B_6 (75 mg), B_1 (150 mg), B_{12} (75 µg), E (300 mg) and E (1200 I.U.). Patients with alkalinizing urinary tract infections were given up to 1.5 g of vitamin C daily. Those with demonstrable Mg deficiency were given 300 mg Mg^{++} as the hydroxide or a chelate, depending on the patient's bowel habits. All were also given a therapeutic vitamin-mineral formulation daily. In each instance, d-penicillamine was started with a single 250 mg capsule daily, with the dose increased by one capsule/day (at no less than one mo intervals) until a total daily dose of 2 g was reached (given in divided doses, an hr before meals and at hr of sleep). If improvement was not sustained, the dosage was raised to 2.25 g/day. When the penicillamine is started zinc gluconate is given with meals (10 mg Zn^{++}). When the penicillamine dosage exceeds 1 g/day, the total daily Zn is increased to 45 mg and the pyridoxine to 150 mg. Patients with malabsorption are given Mg and B vitamins parenterally at weekly intervals.

Complete blood counts are performed twice monthly for the first few mo and monthly thereafter. Urinalysis for protein and cells is done twice monthly. The patients are examined regularly for rash or signs of skin friability and queried as to appetite, loss of sense of taste, dyspepsia or other unusual manifestations.

RESULTS

Among the 48 patients treated for short to long periods (Table IA) there were 2 side effects that were reversible with Zn therapy and 2 minor early transient rashes. Of 3 renal problems that might have been caused by d-penicillamine, one (proteinuria) was in a patient with a history of penicillin anaphylaxis. He cleared on discontinuation of therapy and was not rechallenged with the drug. There were 2 instances of transient hematuria, the etiologies of which are uncertain, kidney biopsies having been refused. One, who was leaving the hospital, had therapy discontinued. The other is being maintained on low dosage therapy without recurrence of hematuria.

These results are in sharp contrast to the published incidence of side effects with d-penicillamine (Table IB). The evidence of acute, usually early, side effects had ranged from 10-30% (Table II). Acute adverse reactions (pruritus, skin rash and drug fever, often associated with eosinophilia, and of nausea and vomiting) were associated with intolerance of d-penicillamine and early discontinuation of therapy in about half of the rheumatoid arthritis patients given d-penicillamine, until it was found that increasing d-penicillamine dosage gradually (by 250 mg/d at 2-4 wk intervals) (9, 27, 44) reduced their incidence. Neutropenia, or aplastic anemia, has been reported, is not dose or time related and is considered idiosyncratic (27, 50, 60) or a manifestation of acute sensitivity (60). Numerous granulocyte precursors were found in the bone marrow in one case (6). However, both fatal and reversible cases of aplastic anemia have been reported (2-4, 40, 56), most in patients who had previously or concurrently received other drugs that cause blood dyscrasias (4, 8, 40, 56) or who had full dosage restarted in a double-blind crossover study (3). These events have led to recommendations that patients previously given gold salts or phenylbutazone be considered at

high risk of marrow reactions (8, 65) and that complete cessation of d-penicillamine be avoided, if possible, in patients whose clinical improvement might be dependent on its use, should the adverse reaction be controllable (52).

TABLE I. A. INCIDENCE OF ADVERSE REACTIONS WITH COMBINED d-PENICILLAMINE AND NUTRIENTS

	Patients	Serious Possible Side Effects	Minor Side Effects
>12-40 months d-penicillamine (2-2.25 g/d)	18	1) Painless hematuria--transient; on restarting R_x	1) Ecchymoses--early (responded to Zn) Ecchymoses--recurred on 2.75 g/d (↓ with ↓ dosage)
6-12 months R_x (1-2 g/d)	13	1) Painless hematuria--intermittent--possibly 2° to d-pen	
<6 months R_x (250-1250 g/d)	17	1) Proteinuria--in patient with penicillin anaphylaxis probably 2° to d-pen	1) Taste loss--early (responded to Zn) 2) Faint transient rash
Total = 48		2 (Possible to probable) 2 (Unlikely)	2 (Definite) 2 (Possible)

B. COMPARISON OF INCIDENCES OF ADVERSE REACTIONS

	Present Study (48 Patients)	Published Reports (d-Penicillamine)
Acute: Rash, Pruritus, ↓WBC-	1 (+ 1 ?)	-- 10-30%
Taste Loss----------	1 (before Zn)	-- 20-40%
Ecchymosis----------	1 (↓ with Zn)	-- on high dosage
Proteinuria*----------	1** (+ 1 ?)	-- 33%
Hematuria*----------	1*** (+ 1 ?)	-- Occasional
Thrombocytopenia*----------	0	-- Preceding serious reactions
Goodpasture Syndrome*------	0	-- Rare
Lupus-like Syndrome*-------	0	-- Rare
Myasthenia Gravis*---------	0	-- Rare
Aplastic Anemia*----------	0	-- Rare

*Serious reactions **in patients with pencillin-anaphylaxis
***cause not certain (no renal biopsy)

TABLE II. ACUTE REACTIONS TO d-PENICILLAMINE
(Usually early)

Rash (10-30% incidence)*	Anorexia	No difference
Pruritus*	Nausea	In placebo and
Drug Fever*	Vomiting	Drug groups
Urticaria*	Dyspepsia	(Double-blind)
Neutropenia*,**	Mouth ulceration**	

Taste Blunting (20-40% incidence)
(Prevented by zinc supplements)

*Less common with gradually increasing doses
**More common with dl-penicillamine - - - -? Role of B_6 inhibition

Side effects that are related to long term, high dosage therapy are listed in Table III; they are reversible when the dosage is lowered (60). Some have been corrected by Zn repletion (31). The serious side effects that include auto-immune reactions have been reported predominantly in patients with rheumatoid arthritis (Table IB). They usually develop after a year of therapy (27). The renal complication, which can result in serious damage unless the regimen is altered, is heralded by proteinuria (8-10, 16, 19, 25, 27, 30, 35, 50, 51, 58, 60) or rarely by hematuria (10, 51, 60, 61); the latter has been accompanied by hemorrhagic pneumonitis and proven fatal (60, 61). Renal biopsy studies have shown thickening of the basement membrane of Bowman's capsule by deposition of immunofluorescent material, providing proof of immune-complex disease (16,19, 25,27,30, 35, 50, 58, 60). Since glomerular lesions (1) and abnormal renal metabolism (46) have been produced by vitamin B_6 deficiency in rats, and because pyridoxine is inactivated by penicillamine (by formation of thiazolidines) (28, 33), this chemical reaction might be contributory to the renal damage of patients on long-term penicillamine therapy (54, 59). The fact that rheumatoid arthritis patients have abnormal tryptophan metabolism (28, 57), possibly due to functional pyridoxine deficiency (13), suggests that their susceptibility to renal damage while on penicillamine therapy might be contributed to by its interference with pyridoxine's activity. Although we have given pyridoxine to our patients receiving high dosage penicillamine therapy, we cannot attribute their very low incidence of adverse reactions only to prevention of vitamin B_6 deficiency. We have also corrected other demonstrated nutrient deficiencies and prevented Zn depletion.

TABLE III. ADVERSE REACTIONS TO d-PENICILLAMINE
(associated with long-term, high dose R_x)

Result of effects on skin	Collagen
	Elastin
	Keratin
Easy brusing*	
Hemorrhage into skin*	
Blood blisters at pressure points	
Elastosis perforans	
Parakeratosis*	

*Possibly related to zinc depletion

Our first (cirrhotic) patients having shown unusually prompt subjective and objective improvement when d-penicillamine was added to the nutrients (which they were given while we awaited clearance for this use of d-penicillamine), our initial objective was to determine whether the use of the vitamins which are anti-oxidant, sulfhydryl (SH) - protective agents (12, 32, 37, 41, 45, 49, 53, 62) might permit use of lower doses of d-penicillamine. For example, in Wilson's disease some of the metabolic improvements from the use of d-penicillamine have been attributed to its free SH-group (64). We thus initially kept the patients on no more than 500-750 mg/day for several months, until recurrence of signs and symptoms predicated further increases in dosage. During our more than 3 years' experience, we have found that we could rarely sustain the improvement on less than 2 g daily; several patients required 2.25 g daily, and one required increase to 2.75 g temporarily, until development of ecchymoses necessitated reduction of his dosage to 1.75 g daily.

Because most of our patients under treatment have diseases with auto-immune components--hepatic cirrhosis (11) and multiple sclerosis (47)--we anticipated an incidence of adverse effects comparable to those encountered with rheumatoid patients on d-penicillamine. Therefore we instituted frequent laboratory testing to detect d-penicillamine toxicity without delay: urinalysis and complete blood counts twice monthly the first few months on d-penicillamine and monthly thereafter. Additional tests appropriate to the disease were performed to evaluate clinical response. Our data indicate freedom from early adverse reactions (including neutropenia) and from thrombocytopenia (which may precede aplastic anemia) as well as virtual absence of renal side effects.

We cannot claim that the precise regimen we have employed is necessarily the ideal program. It was developed empirically, the B vitamins and vitamin E having been given to cirrhotic patients whose vitamin E and B-complex deficiencies have long been recognized (36, 48) and which we verified in our own patients. The cirrhotic patients had been on thiamine therapy before this treatment program was started; it was continued as a vitamin that is active in the SH-system (32, 41). Several multiple sclerosis patients had been on parenteral vitamin B_{12}, which is also active in maintaining SH levels (12, 37, 45, 49); thus this preparation was also continued and included in new patients entered into the study. This therapy is indicated in cirrhotic patients who often have pancreatitis, which has been shown to interfere with B_{12} absorption (39). All chronically ill patients should receive a therapeutic vitamin-mineral complex. If specific deficits persist or develop they must be corrected. With vitamins and minerals, we are dealing with essential elements that cannot be deleted from a patient's regimen to achieve purity of experimental design. It is important to give d-penicillamine at a time separate from pyridoxine, which it inactivates (28, 33) and from Zn, which it chelates (34).

We have recently discovered that our patients on long term full-dosage d-penicillamine therapy are Cr depleted, and that several who had had normal glucose tolerance curves and pyruvate and lactate levels at the outset of our study now have diabetic curves and hyperinsulinemia in response to a glucose tolerance test. This is under further investigation. Several are being supplemented with brewers' yeast, a good source of Cr as glucose tolerance factor (42).

CONCLUSION

d-Penicillamine, useful in Wilson's disease and heavy metal poisoning because of its metal chelating activity, and in cystinuria because of its formation of soluble mixed disulfides of cystine, has been increasingly recognized as toxic since its utilization in such auto-immune diseases as rheumatoid arthritis. The mineral and vitamin deficiencies of cirrhotic

patients justified their administration before and concurrently with d-penicillamine. Pyridoxine was given to correct the existing deficiency and to protect against its intensification by d-penicillamine. Zinc was given to correct the existing deficit in cirrhotics and because Zn depletion has developed with use of d-penicillamine. SH-protective vitamins (E, B_1, B_{12}, C) were given to enhance the metabolic effects of the SH-donor, d-penicillamine, and to correct existing deficiencies. Magnesium was given to correct its deficit, which is well known in alcoholic and cirrhotic patients, and which we detected in most of our chronically ill patients. When d-penicillamine was added to the nutritional regimen in our first (cirrhotic) patients, there was surprisingly rapid improvement. Thus, the same treatment regimen was instituted in patients with other chronic, progressive diseases. Unexpectedly, very few side effects were seen in almost 50 patients, despite use of 2 g/day or more of d-penicillamine in many for 1-3 years. This contrasts with the incidence of adverse reactions that necessitate discontinuation of treatment in 1/3 of rheumatoid arthritis patients. Whether it is the use of the entire complex of nutrients or of just those that are removed or inactivated by d-penicillamine, or that are notably deficient at the outset, requires further study.

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DISCUSSION

Inquirer: William B. Pratt, Veterans Administration Hospital, Albuquerque, NM

Q. Do you know the method of action of d-Penicillamine in disease?

A.

	Activities	Application
1.	Chelation of copper heavy metals	Wilson's disease - heavy metal poisoning - hepatic cirrhosis (with high hepatic levels of Cu)
2.	Formation of soluble mixed disulfides with cystine	Cystinuria
3.	Enhancement of collagen turnover	Hepatic cirrhosis; scleroderma
4.	Depolymerization of macroglobulins	Waldentron's disease (originally applied to rheumatoid arthritis on this basis)
5.	Anti-autoimmune activity; subsidence of lymphoid nodules	Rheumatoid arthritis; chronic active liver diseases; chronic hepatitis; acute alcoholic hepatitis (?); multiple sclerosis (?)
6.	Anti-viral activity (RNA: i.e. polioviries)	