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LOW DOSE PENICILLAMINE IN SYSTEMIC SCLEROSIS: IS IT EFFECTIVE?

NISKIE DAWKI PENICYLAMINY W TWARDZINIE UKŁADOWEJ: CZY SĄ EFEKTYWNE?

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Abstract
Low dose D-penicillamine 150mg was given on alternate days to 23 patients of limited cutaneous systemic sclerosis (lcSSC) and 5 of diffuse cutaneous systemic sclerosis (dcSSC) subtypes. Modified Rodnan scoring remained unchanged in 19 and progressed in 3 patients of lcSSc. Only 1 female showed a decrease in the score. In the dcSSc, score decreased only in 1. She had a baseline score of 12 which went down to 4. No new systemic activity was seen in her.

Streszczenie
Niską dawkę D-penicylamine 150mg otrzymywało co drugi dzień 23 pacjentów z ograniczoną skórną postacią twardziny układowej (lcSSc) i 5 pacjentów z rozlaną skórną postacią twardziny układowej (dcSSC). Zmodyfikowana punktacja Rodnan pozostała niezmieniona w 19 przypadkach a postępowała u 3 chorych z lcSSc. Tylko jedna kobieta wykazała spadek w punktacji. W dcSSc, wynik zmniejszył się tylko w 1 przypadku. Pacjentka z 12 punktów bazowych ostatecznie otrzymała 4 punkty. Obserwowano u niej brak nowej ogólnoustrojowej aktywności choroby.

Key words: systemic sclerosis; D-penicillamine; skin diseases
Słowa klucze: twardzina układowa; D-penicylamina; skin diseases

Introduction

Systemic sclerosis is a multi systemic disorder with the cardinal features of Raynauds phenomenon, sclerosis of skin with or without internal organ fibrosis. The basic pathology is believed to be vascular endothelial damage, autoimmunity and increased deposition of insoluble collagen in tissues. The ideal treatment remains elusive. D- penicillamine, a copper chelating agent used in Wilsons Disease, has been seen to block the aldehyde groups involved in the inter- and intra- molecular bonding of collagen helices [1]. This results in the formation of more soluble collagen. D- penicillamine also promotes enzymatic degradation by collagenase enzyme [1]. It has independent immunological effects as well [1]. D- penicillamine at a high dose has been tried for systemic sclerosis [1]. However, laboratory monitoring at this dose is cumbersome and many side effects are seen [2]. Recently low dose penicillamine 125 mg on alternate days has been found to be as effective as high dose therapy with lesser side effects [3-5].

Aim of the study

To report our experience with low dose D- penicillamine 150mg on alternate days for 2 years in Systemic Sclerosis (125mg tablet was not available).

Materials and Methods

This study was carried out in the Department of Dermatology SMHS Hospital (Associated teaching hospital of Government Medical College, Srinagar) between 2005-2010. All the patients of systemic sclerosis registered during this time period (both newly diagnosed as well as follow-up cases) were evaluated. Particular attention was paid to the skin sclerosis in each. Modified Rodnans Skin Scoring (mRSS) system was used to evaluate the extent of skin sclerosis [5]. 17 sites were evaluated: face, anterior chest, anterior abdomen, bilateral sites of upper arm, forearm, dorsum of hands, fingers, upper legs, lower legs, dorsum of foot. Scoring given was 0 if no change was seen, 1-skin thickened, 2-moderately involved cannot be pinched, 3-severely involved cannot be moved. Scoring was done at baseline and in patients put on low dose Penicillamine was repeated at 6 months, 1 year, 18 months, and 24 months. In order to reduce inter observer error, the same observer did a repeat scoring evaluation as far as possible.

The diagnosis of systemic sclerosis was made on the basis of the ARA criteria. A complete history especially regarding the presence of Raynaud's phenomenon, dysphagia, and dyspnoea was taken into account. A detailed physical examination including recording the weight, pulse, and blood pressure, and examination of chest (measuring the chest expansion and auscultation for basal crepitations), cardiovascular system, and abdomen were done. This was followed by a meticulous cutaneous examination. Next the patients were submitted to a battery of investigations including complete hemogram with erythrocyte sedimentation rate [ESR (fasting)], renal function tests (KFT), blood sugar (fasting), estimation of serum electrolytes, liver function test (LFT) with enzymes, chest X-ray [CXR (PA view)], electrocardiogram (ECG) all leads, X-ray hands and feet bilaterally, and urine analysis. Before starting therapy, a representative skin biopsy from fingers was sent for histopathological examination. Ophthalmological checkups for ocular tension and visual acuity was done along with upper GI endoscopy or barium swallow, high-resolution CT scan (HRCT), 24-h urinary protein, creatinine clearance, electromyography, echocardiography, pulmonary function tests (PFT), stool for occult blood, serum iron, and total iron binding capacity (TIBC). A complete collagen vascular profile was done: VDRL, LE cells, ANA, RA factor, anti-ds DNA, anti-RNP, anti-topoisomerase, anti-centromere, and creatinine phosphokinase (CPK) levels. All these investigations were done at baseline. CBC with ESR, KFT, urine exam, and BP recording was done monthly; 24-h urinary protein and CXR were repeated in 6 months. Carbon monoxide diffusion capacity could not be measured due to the nonavailability of facilities for the same.

Results

A total of 63 patients of systemic sclerosis registered for this study. Of these 54 were of limited cutaneous systemic sclerosis (lcSSC) subtype and 9 were of diffuse cutaneous systemic sclerosis (dcSSC). In lcSSc subset, 23 patients had no oesophageal involvement and mRSS of >= 2). In dcSSc, 4 patients had pulmonary involvement at the time of admission as indicated by moderate to severe restriction on PFT. Hence D Penicillamine was given to 23 patients of lcSSc and 5 of dcSSc subtypes. Score remained unchanged in 19 and progressed in 3 patients of lcSSc. Only 1 female (23years old with disease of 6 years duration showed a decrease in the score (from 5 to 2). However, the pinched appearance of nose persisted. In the dcSSc score decreased only in 1. She had a baseline score of 12 which went down to 4. No new systemic activity was seen in her. Incidentally this patient had been on Dexamethasone pulse therapy previously >1 year back and had developed genitourinary tuberculosis due to the same. Duration of disease in her was 7 years. In two patients with mild restriction in PFT at baseline the skin sclerosis progressed and pulmonary function tests showed a worsening. In one patient (a twenty four year old female with hyper pigmentation and skin sclerosis of five years duration) the mRSS worsened from 14 to 24. No new internal activity was however noticed. In one patient (a 35 years old female with four years history of sclerosis and Raynauds phenomenon) followup was poor. She continued to take therapy for 4 years. She reported back with severe skin sclerosis, anaemia, weight loss and pulmonary involvement in the form of severe restrictive lung disease. She had been previously on Dexamethasone pulse therapy and had developed cervical lymphadenopathy. Present investigations revealed pulmonary tuberculosis. Patient was put on antitubercular therapy and was planned to be put on cyclophosphamide later on.

Discussion

The role of D penicillamine in the treatment of systemic sclerosis in various studies was believed to be primarily on Skin Sclerosis with no effect on visceral and vascular symptoms but a few studies claim its efficacy on pulmonary fibrosis [6].Vital capacity and Forced expiratory volume improved but the Diffusion Capacity for carbon monoxide remained unchanged. The effect on skin sclerosis is believed to be not foolproof and its irreversibility is doubtful. Whether it prevents or retards internal organ involvement is also not fully known. As it is believed that extent of skin sclerosis has prognostic significance and it reflects internal organ involvement the therapy assumes importance in this multi system disease [5]. Penicillamine has to be started at a low dose of 250 mg and may have to be gradually increased to 1150mg/day with each dose increment being gradual. Monitoring for side effects is mandatory. In a study by Steen et al, Penicillamine 635mg for 1.8 years was studied [2]. 47% patients had side effects in the form of rash, proteinuria, gastro- intestinal symptoms, dysgeusia, oral ulcers, thrombocytopenia, neutropenia, myasthenia gravis and pemphigus. 29% patients discontinued treatment due to toxicity. Recently it was seen that 125mg penicillamine on alternate days was as effective as high dose therapy, with no advantage achieved on increasing the dose beyond this [3-5]. The recommended duration of low dose therapy is 2 years. Maximum effect is seen in rapidly progressive diffuse cutaneous SSc of less than two years duration [7].

The therapy of this unpredictable disease should serve the following purpose:

Does it decrease skin sclerosis?

Is this decrease maintained on discontinuation of therapy?

Does it prevent or retard pulmonary fibrosis?

Does it prevent development of renal crisis?

Does it decrease new organ involvement?

Hence while on therapy, lookout for fresh activity over baseline was done. In view of this low dose regimen being claimed as being relatively non-toxic we decided to try it in lcSSc without oesophageal involvement and in all dcSSc without internal organ involvement other than mild pulmonary restriction. However, a recent study proves that even low dose penicillamine therapy is not blameless vis a vis the side effect profile [8].

There were limitations in our study as 125mg capsule was not available and we had to use 150 mg instead. Even though low dose penicillamine is recommended only in rapidly progressive dcSSc, we gave it to lcSSc also without oesophageal involvement and dcSSc without systemic involvement irrespective of the duration of therapy the rationale being that therapeutic option in SSc are limited. Skin sclerosis indicates internal organ involvement. Penicillamine affects skin sclerosis and low dose is relatively safe. lcSSc is also a systemic disease with oesophageal and pulmonary vascular involvement. Hence reversal of skin sclerosis would infer retardation of internal organ involvement.

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