

Is d-penicillamine an effective treatment for a patient with scleroderma of the diffuse cutaneous systemic sclerosis subtype?

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Citation

C Simas. *Is d-penicillamine an effective treatment for a patient with scleroderma of the diffuse cutaneous systemic sclerosis subtype?*. The Internet Journal of Academic Physician Assistants. 2009 Volume 7 Number 2.

Abstract

Diffuse cutaneous systemic sclerosis is a complex disease that can affect multiple organ systems. Treatment involves various classes of medications and sometimes a trial and error method to determine what works best for each individual patient. Fibrosis of the skin is usually the earliest manifestation of the disease and many different treatments have been used. One of these treatments is d-penicillamine. This evidence based paper reviewed two studies that were conducted in attempts to determine if d-penicillamine is an effective treatment for patients with diffuse cutaneous systemic sclerosis. The two studies reviewed both produced results that showed that d-penicillamine was able to cause improvements in scleroderma patients. It was concluded from the research that d-penicillamine is an effective option for physicians to consider, but further studies should be conducted on this topic.

INTRODUCTION

Scleroderma is a connective tissue disease that is classified as one of the autoimmune rheumatic diseases. Currently it is estimated that 300,000 Americans have the diagnosis of scleroderma and approximately one third of those patients experience systemic symptoms.¹ Scleroderma causes a hardening of the skin and can affect many of the body's organ systems, most notably the GI tract, heart, lung and kidneys. The exact cause of scleroderma is still unknown and there is no curative treatment available at this time. Therefore, it is important that research be done to discover treatments that will help alleviate symptoms and slow the progression of this sometimes debilitating disease. D-penicillamine is one drug that has been researched over the years to determine its effectiveness in treating scleroderma and studies have produced varied results. This paper will evaluate the research currently available on d-penicillamine and advise health care providers on the value of its use in scleroderma treatment.

BACKGROUND

Scleroderma is an autoimmune connective tissue disease that is characterized by fibrosis of both the skin and the internal organs. There are 300,000 people in the United States with scleroderma, which means that one out of every 906

Americans is currently suffering from this disease.¹ As with many autoimmune conditions, scleroderma is more commonly found in women than men. The average age of onset of the disease is between 25 and 55 years old.¹ The presentation of scleroderma is widely varied and the disease can be broken down into multiple subtypes. The first division is into the two major types of scleroderma; localized scleroderma and systemic sclerosis. There are two forms of localized scleroderma. One is linear scleroderma which commonly occurs in childhood and causes "abnormalities of the skin and subcutaneous tissues with often follow a dermatomal distribution and are found predominately on one side of the body."² The other form of localized scleroderma is morphea, which is characterized by patches of sclerotic skin that develop on the limbs and trunk of the body.² Systemic sclerosis, as the name implies, has a more extensive effect on the body and manifests in two different forms; localized cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis. Patients with localized cutaneous systemic sclerosis tend to have sclerosis of the skin on the hands, neck and face. "They also have prominent vascular manifestations and may suffer from CREST syndrome."² Patients with diffuse cutaneous systemic sclerosis have widespread sclerosis of the skin and "are at a greater risk for the development of significant renal, lung

and cardiac disease.”²

The exact cause of scleroderma is still not completely understood, but researchers do have some theories. “Most current hypotheses of the pathogenesis of systemic sclerosis focus on the interplay between early immunological and vascular changes.”³ These changes result in a large number of activated fibroblasts that produce excess amounts of extracellular matrix and collagen. This deposition of increased amounts of collagen in the skin and the synthesis of excessive extracellular matrix are key components in the development of scleroderma. There are many other factors that play a role in scleroderma at the cellular level. It is theorized that the vasoconstrictors nitric oxide and endothelins (the most potent vasoconstrictor known) are important in the vascular and endothelial changes seen in scleroderma.³ Changes to the immune system are also thought to be a part of the development of scleroderma. “The continuing activation of endothelial cells resulting in the up-regulation of adhesion molecules, leukocyte adhesion and leukocyte migration out of the vasculature probably contributes to the pathogenesis of systemic sclerosis.”³ Also seventy-five percent of patients with scleroderma have autoantibodies in the blood against a number of antigens.³ These autoantibodies have been found to react to topoisomerase I, centromere antigens, fibrillarin and RNA polymerase. These factors, along with others, are all thought to be a part of pathogenesis of scleroderma.

The diffuse cutaneous systemic sclerosis form of scleroderma can affect many of the body’s organ systems and therefore, has a wide variety of symptoms. The skin is usually affected first and presents as a thickening and hardening of the skin. The face, hands and fingers are generally the earliest areas of the body involved. Some other symptoms involving the skin are pruritis, edema, sclerodactyly and digital ulcers. As the disease progresses the skin on the arms, chest and abdomen also become affected. The blood vessels are also affected in systemic sclerosis. “The most obvious clinical manifestation of vascular dysfunction is Raynaud’s phenomenon, defined as sequential color changes in the digits precipitated by cold, stress or even change in temperatures.”⁴ Of the organ systems involved, the gastrointestinal tract is the most common. Almost ninety percent of patients have some degree of gastrointestinal involvement.⁴ Any part of the GI tract from the mouth to the anus can be affected; usually esophageal hypomotility and incompetence of the lower

esophageal sphincter develop first with symptoms of dysphasia, coughing after swallowing and gastroesophageal reflux. Vascular ectasia in the stomach may also develop, which can cause GI bleeding and anemia.⁴ The kidneys are also commonly affected and “sixty to eighty percent of patients with diffuse cutaneous systemic sclerosis have pathological evidence of kidney damage.”⁴ Most patients with kidney damage develop proteinuria and hypertension, however ten to fifteen percent will experience what is known as scleroderma renal crisis, which is the sudden onset of acute renal failure.⁴ Cardiac complications of scleroderma include pericarditis, pericardial effusion, heart failure and arrhythmias. Patients who develop cardiac involvement tend to have a poor prognosis. “Pulmonary involvement is seen in more than seventy percent of patients with systemic sclerosis,” the most common manifestations being, “interstitial lung disease and pulmonary vascular disease, leading to pulmonary arterial hypertension.”⁴ Diagnosis becomes difficult because there are so many possible presentations of the disease.

The diagnosis of scleroderma can be lengthy process. The large variety of symptoms can make it difficult to initially pinpoint the exact cause. The list of differential diagnoses early on includes eosinophilic fasciitis, graft versus host disease, reflex sympathetic dystrophy, lupus and amyloidosis³ as well as many other conditions based on the patient’s presenting symptoms. There are multiple laboratory tests that are performed to help make the diagnosis of scleroderma. One test that is usually performed early on is a blood test for antinuclear antibodies (ANA). ANA titers are almost always positive in patients with scleroderma and usually the titers are very high. However, positive ANA titers are not specific to scleroderma and they only help to limit the differential diagnosis. There are two antibodies that can be tested for that are specific to scleroderma and are helpful in making a diagnosis. These are, topoisomerase I antibodies, also known as SCL-70, which are found in 30% of patients with diffuse systemic sclerosis and an anticentromere antibody, which is found in 80-90% of patients with limited disease.⁴ These blood tests, along with the clinical picture, are what is available to make the diagnosis of scleroderma. Normally a patient is seen by both a dermatologist and a rheumatologist before the proper tests are ordered, all the information is put together and a diagnosis is made. Once the patient has the correct diagnosis, treatment needs to be started.

There is currently no curative treatment available for scleroderma, so most health care professionals focus on treating the symptoms as they develop. For Raynaud's phenomenon, calcium channel blockers, like nifedipine and amlodipine, are used to relax the smooth muscle cells in the blood vessels and prevent vasoconstriction. For symptoms of GERD due to lower esophageal sphincter incompetence, H-2 blockers like ranitidine and proton pump inhibitors like omeprazole are used. GI stimulants such as metoclopramide are used to treat difficulty swallowing due to esophageal hypomotility. The first line treatment for a scleroderma patient with hypertension is an ACE inhibitors to provide protection for the kidneys. ACE inhibitors are also used first line with severe hypertension due to scleroderma renal crisis. Interstitial lung disease in patient with scleroderma is also treated with the immunosuppressive agents cyclophosphamide, cyclosporine and azathioprine.

Sclerosis of the skin is the most common symptom of the disease, but it has proven rather difficult to treat. Immunosuppressants, such as cyclophosphamide, methotrexate and d-penicillamine, are effective treatments for rheumatoid arthritis and are often used in scleroderma treatment, despite not being FDA approved. These drugs have been shown to offer some improvement in the hardening and tightening of the skin. Cyclophosphamide is "derived from nitrogen mustard and works to decrease the levels of circulating T and B cells."⁶ This causes a decrease in inflammation and seems to help with the skin symptoms of scleroderma. Methotrexate is a folic acid antagonist. The inhibition of folic acid causes a leukocyte suppression, which in turn causes a decrease in inflammation.⁶ Again, it's the decrease in inflammation that is thought to be what causes the improvement in the hardening and tightening of the skin. D-penicillamine is an immunosuppressive agent that happens to be a metabolite of the antibiotic penicillin, but has no properties of an antibiotic. D-penicillamine is used as a treatment for rheumatoid arthritis when other methods have failed. It works in rheumatoid arthritis by reducing the numbers of T-lymphocytes, inhibiting macrophage function, decreasing interleukin-1, decreasing rheumatoid factor, and preventing collagen from cross-linking.⁶ D-penicillamine is also used to treat Wilson's disease. It is a chelating agent that is able to remove excess copper from the body. D-penicillamine "was first suggested as a potential treatment for systemic sclerosis following the observation that patients with Wilson's disease treated with the drug showed remarkable thinning of the skin

accompanied by a reduction of total skin collagen."⁷ D-penicillamine is not FDA approved in the treatment scleroderma and multiple studies have been conducted to determine if it is an effective form of treatment for a patient with scleroderma of the diffuse cutaneous systemic sclerosis subtype. This evidence based medicine paper will review two of those studies.

METHODS

This paper asks the question, "Is d-penicillamine an effective treatment for a patient with scleroderma of the diffuse cutaneous systemic sclerosis subtype?" This is a treatment question and it is best answered by a meta-analysis or a randomized controlled clinical trial, which are level I evidence, or a cohort study which is level II evidence. A systematic search was conducted to find articles that evaluated the efficacy of d-penicillamine as a treatment for scleroderma of the diffuse cutaneous systemic sclerosis subtype. Medline with full text, PubMed/Medline and Science Full Text Select were searched using the key words "scleroderma treatment", "d-penicillamine treatment" and "scleroderma AND d-penicillamine". Inclusion criteria incorporated peer-reviewed articles that were full text, of all levels of evidence, articles written in English and those that involved human subjects. Articles published after 1980 were included; this is because there is little available research on scleroderma and its treatment. Abstracts of the articles generated by the search were reviewed to determine if the information they contained would be helpful in answering the question proposed. Papers were chosen if they contained statistical analysis about how to predict the efficacy of treatment with d-penicillamine. The two articles used for this paper were found on Medline with full text and are evidence based medicine papers. One article is a case study published in 2008 and the other is a prospective cohort study that was published in 1982.

DISCUSSION

The first article is entitled "A retrospective randomly selected cohort study of D-penicillamine treatment in rapidly progressive diffuse cutaneous systemic sclerosis of recent onset" written by Derk, Huaman and Jimenez.⁷ It is a case study that was published in 2008. The goal of the study was to determine the efficacy of d-penicillamine as a treatment for scleroderma. The researchers found 392 patients with diffuse cutaneous systemic sclerosis who were treated at the same institution between 1987 and 2002. Of these 392 patients, 50 were eliminated because of previous use of d-

penicillamine or contraindications to the use of d-penicillamine. The remaining 342 patients had all received at least 3 months of d-penicillamine at escalating doses, starting at 250mg a day and slowly increasing over two weeks time to 1250mg daily if tolerated. "From the 342 patients, 150 patients were randomly selected using a computer randomization program to avoid inherent selection biases."⁷ Those 150 patients were narrowed down even further using inclusion and exclusion criteria. Inclusion criteria were "time from onset of skin sclerosis to initiation of d-penicillamine being less than 24 months, extent of skin sclerosis involving the trunk and/or arms and legs, no previous treatment with d-penicillamine or other immunosuppressant agent and systemic sclerosis with progressive skin involvement."⁷ Exclusion criteria were "skin involvement confined to the face or acral regions of the body and chemically induced scleroderma, diffuse fasciitis or mixed connective tissues disease."⁷ Eighty-four patients met the inclusion and exclusion criteria and were included in the study. At the beginning of treatment, the extent and severity of the skin involvement was assessed by the modified Rodnan skin score (MRSS) which evaluated the skin by palpating skin thickness in 17 areas of the body with a maximum score being 51. The rule of nines was used to measure the total body surface (TBS) affected by the disease and lastly, the Medsger systemic sclerosis severity scale was used to measure the severity of organ involvement. These tests were also performed during treatment with d-penicillamine and at the end of therapy.

The study found that d-penicillamine showed clear therapeutic benefit in the treatment of diffuse cutaneous systemic sclerosis. At the initiation of d-penicillamine therapy "the mean extent of TBS affected by clinically detectable sclerodermatous involvement was 30.9% and the MRSS was 19.9%. The researchers found that skin involvement continued to worsen during the initial months of treatment so the maximum mean TSB skin involvement was 40.4% and the maximum mean MRSS was 25.0%. These peaks were reached at about 5 months into treatment. "The first signs of clearly detectable skin improvement were noted at a mean of 10.6 months following d-penicillamine initiation."⁷ By the end of the study the TSB involvement was reduced from 40.4% to 18.1% and the MRSS was reduced from 25.0 to 13.9. "Both reductions reached statistical significance."⁷ However, nineteen patients did not have any skin improvement with the d-penicillamine treatment. Also, at the end of the study, based on the

Medsger severity scale, it was determined that "there was statistically significant improvement in pulmonary, renal and cardiac involvement."⁷

This article was well researched by the authors, provided information that was accurate and helpful and was published in a peer-reviewed journal. There was no bias noted in the article and the authors answered the question they proposed in the beginning of the paper. The patient population studied included more females than males, which matches the natural gender distribution of the disease. The researchers explained their methods in a way that was easy to understand and the results were clear. A large portion of the article was dedicated to explaining how they were able to quantify the results using three different clinical measurement scales. One flaw in this study is the small number of patients that the researchers had to choose from. A small group of patients prevents any diversity in the population. The authors recognized that when trying to determine the efficacy of a treatment, a randomized, double-blind placebo-controlled clinical trial is the best research method to use. They then went on to explain that because of the rarity of systemic sclerosis it is difficult to find a large enough patient population to conduct this type of study. Despite this, the researchers firmly believe that their results show that d-penicillamine offers statistically significant therapeutic and clinical benefits to patient with systemic sclerosis.

The second article is entitled "D-penicillamine Therapy in Progressive Systemic Sclerosis (Scleroderma)" and is written by Steen, Medsger and Rodnan.⁸ It is a prospective cohort study that was published in 1982. The goal of this study was to determine the effect of at least six months of d-penicillamine therapy on diffuse cutaneous systemic sclerosis. Between 1972 and 1981, the researchers identified 530 new patients at their clinic with scleroderma and 238 of those patients had diffuse cutaneous systemic sclerosis. Inclusion criteria for the study were "patients with diffuse scleroderma, duration of symptoms less than three years at the time of first evaluation and survival for a minimum of six additional months after evaluation."⁸ The sole exclusion criterion was patients who had already developed kidney disease or developed it within 6 months of the initial evaluation. Based on these criteria, 120 patients were excluded and 118 patients were eligible for the study. Of those 118 patients, seventy-three had already received at least 6 months of d-penicillamine therapy and were placed in the study group. The other forty-five patients had never been

treated with d-penicillamine and were placed in the comparison group. The patients in the comparison group did not receive d-penicillamine during the study, but were allowed to continue with any other medication they were on, such as “colchicine, azathioprine or vasodilators.”⁸ The researchers quantified the degree of skin thickening by estimating the skin thickness at 26 areas of the body on a scale of zero to four, giving the skin scale a maximum score of 104. The researchers also measured “the distance between the third fingertip and the distal palmar crease (finger to palm distance) in full flexion as an indicator of contracture.”⁸ The patients in the d-penicillamine group continued to be treated with the drug for an average of twenty-four months and were given an average dose of 750mg a day. Patients in both groups were all re-evaluated at three different intervals (6-18 months, 19-42 months and over 42 months) to determine the change, if any, in degree of skin thickening and contracture of the skin.

The study found that long-term therapy with d-penicillamine did produce improvements in patients with diffuse cutaneous systemic sclerosis. “The reduction in total skin score in the d-penicillamine group was greater than that in the comparison group.”⁸ In fact, the total skin score improved by 25% or more in 34 out of 73 patients in the d-penicillamine group compared to the 9 out of 45 patients in the control group who showed a 25% improvement. Also, “forty-seven patients treated with d-penicillamine had a mean reduction of 0.4cm in finger-to-palm distance after treatment” compared to the “twenty-one patients in the comparison group who has a mean increase of 0.2cm in the measurement.”⁸ This indicates that there was less contracture in the patients treated with d-penicillamine. However, this difference was not statistically significant. In terms of visceral organ involvement, the researchers identified, at the beginning of the study, twenty-four patients in the d-penicillamine group and sixteen patients in the comparison group at risk for developing GI involvement. The patients were considered to be at risk for developing GI involvement because they showed no signs of GI organ damage at the beginning of the study. Only two out of those twenty-four patients in the d-penicillamine group went on to develop GI involvement compared to the five out of sixteen patients in comparison group who developed GI involvement. Also, “twelve (16%) of 73 d-penicillamine treated patients had one or more new organs affected” and “in contrast, 15 (33%) of 45 patients in the comparison group had one or more new organs affected.” Lastly, the study showed that the 5 year

survival rate for the d-penicillamine group was 88% and only 66% for the comparison group.

The article was published in a peer reviewed journal, was well researched by the authors and provided helpful and accurate information. The purpose of the study was well defined at the beginning of the article and the study delivered the results it promised. The researchers clearly showed how they determined their study population by explaining their inclusion and exclusion criteria. They also matched the two groups based on age and gender as best as they could. This study of d-penicillamine was the first to only include patients that had progressive and diffuse cutaneous systemic sclerosis and the researchers were very careful to adhere to this. Also, all patients were accounted for in the data that was produced by the study. No bias was noted throughout the article and the authors were quick to point out the limitations of a prospective cohort study, mainly that the patients cannot be randomized. In fact, the conclusion of the article discussed the authors’ belief that the data they collected and the conclusions they drew from it would be enough to encourage other researchers to conduct a randomized double-blind study. There is one major flaw with this study. The researchers did not control what other medications the patients were taking for their scleroderma. This causes uncertainty in the data; it can’t be proven that the improvements were due solely to the d-penicillamine because there were other factors involved.

CONCLUSION

This paper set out to answer the question, “Is d-penicillamine an effective treatment for patients with scleroderma?” The two articles agreed that d-penicillamine appears to offer improvement for patients suffering from scleroderma. The authors behind both studies produced results that showed d-penicillamine treatment led to a reduction in skin involvement. The authors of the first article also concluded that d-penicillamine treatment leads to improvements in renal, cardiac and pulmonary involvement. The authors of the second article showed that the rate of new organ involvement is decreased with d-penicillamine treatment and that life expectancy is increased. In conclusion, based on the evidence that is currently available, d-penicillamine is an effective treatment for scleroderma and health care practitioners should consider incorporating it in the treatment regime of scleroderma patients. However, there were also problems with these studies and the evidence was not of high quality so these recommendations should be

used with caution until more studies are done.

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