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Treatment of primary Sjögren's syndrome with D-penicillamine: a pilot study

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ABSTRACT

Background: Up to now no satisfying systemic treatment is available for patients with primary Sjögren's syndrome.

Methods: In a prospective, open study we investigated the effect of D-penicillamine (first three months 250 mg/day, next three months 500 mg/day) on clinical and immunological parameters in 19 patients with primary Sjögren's syndrome and a mean disease duration of 3.8 years.

Results: Eight patients had to stop treatment mainly due to severe (reversible) loss of taste. Clinically, a statistically significant increase in basal salivary flow was observed after three months ($p<0.05$). In addition, improvement was noted in the Schirmer test and stimulated parotid salivary flow after six months, but these differences were not statistically significant.

Laboratory values showed a decrease in ESR ($p<0.05$) and levels of IgA and IgM (both $p<0.02$) after six months, a decrease in levels of IgA-Rf and IgM-Rf after three months (both $p<0.05$), and an increase in haemoglobin level ($p<0.05$).

Conclusion: From this pilot study we conclude that the treatment of primary Sjögren's syndrome with D-penicillamine has only marginal beneficial effects. Together with its clear side effects this means that D-penicillamine is unsuitable for this indication.

INTRODUCTION

Primary Sjögren's syndrome (PSS) is a systemic autoimmune disease of the exocrine glands, in particular the lacrimal and salivary glands, frequently accompanied by extraglandular symptoms. Polyclonal B-cell activation with production of different autoantibodies such as antinuclear antibodies and rheumatoid factors (Rf) are characteristic serological findings.

Symptoms due to lacrimal and salivary gland involvement can be treated locally. Studies on treatment of PSS with disease-modifying drugs are relatively scarce. A significant reduction in levels of immunoglobulin G and M (IgG and IgM) was seen during treatment with hydroxychloroquine.[1] However, no beneficial effect on clinical symptoms was apparent.[1] Cyclosporin A subjectively improved xerostomia[2] and methotrexate subjectively improved both xerostomia and xerophtalmia as well as arthralgia[3] but no objective effect on clinical symptoms nor an effect on serological parameters was observed. Recently, azathioprine did not show any effect on clinical symptoms or serological findings; in particular, no decrease in levels of immunoglobulins was observed.[4]

D-penicillamine (D-pen) is a disease-modifying drug that has been proven efficacious in the treatment of rheumatoid arthritis (RA). Its mechanisms of action are largely unknown. *In vitro*, D-pen inhibits lymphoblastic transformation induced by polyclonal mitogens and decreases T-cell-dependent production of immunoglobulins by lymphocytes stimulated with Pokeweed mitogen. This inhibitory action is exercised on T lymphocytes. D-pen does not influence B lymphocytes directly.[5,6]

Several publications indicate that treatment with D-pen in

RA lowers the levels of rheumatoid factors, in particular IgM-Rf.[5,7-10] However, no correlation was demonstrated between the decrease in levels of IgM-Rf and the decrease in ESR or clinical disease activity.[7]
In many patients with PSS rheumatoid factors are detectable, frequently at a high concentration. The sublabial and parotid salivary glands have been reported to harbour increased amounts of IgG- and IgM-producing plasma cells.[11,12] It has been demonstrated that rheumatoid factors, antinuclear antibodies and other immunoglobulins are produced locally in the salivary glands of these patients.[13,14] Recently, levels of IgA-Rf were reported to correlate inversely with stimulated parotid flow rate.[15] Although the pathogenic significance of the local and systemic B-cell response is questionable, we may hypothesise from the foregoing data that treatment with D-pen might be beneficial in PSS.
In a Medline search (from 1966 onwards) only one report was found concerning treatment of PSS with D-pen.[16] In all four patients a subjective improvement was seen combined with a lowering of ESR and levels of rheumatoid factors, antinuclear antibodies and gammaglobulin fraction.
The primary objective of this study was to evaluate, in an open uncontrolled study, the clinical and immunological effects of D-pen in the treatment of PSS. Moreover, we evaluated the occurrence of side effects of D-pen treatment in PSS.

PATIENTS AND METHODS

All patients visiting the rheumatology outpatient clinic of our hospital and fulfilling the criteria for the diagnosis of primary Sjögren's syndrome[17] were asked to participate in the study. Exclusion criteria were age <18 years, treatment with cytostatics or disease-modifying drugs during the last six months, use of prednisolone during the last three months, the co-existence of other systemic autoimmune diseases such as RA, SLE and systemic sclerosis, proteinuria >1 g/day, leucopenia $<2.0.10^9$/l, thrombocytopenia $<100.10^9$/l, pregnancy or the presence of childbearing potential without adequate contraception. All subjects gave written informed consent.
The patients started at a dosage of 250 mg D-pen a day, taken half an hour before or two hours after a meal. After three months the dosage was increased to 500 mg a day. At baseline the demographic data and medication used were recorded. In addition, a complete history, physical examination and routine laboratory examinations including whole blood count, renal and hepatic function, and urinalysis were performed. For safety purposes the subjects were seen at three to six weeks intervals to screen for clinical side effects and for measurements of complete blood count and urinalysis. Comedication, if used, was not changed during the study.
The following clinical parameters were assessed at baseline, after three months and after six months: average value of Schirmer test without analgesia (mm/5 minutes; twice on both eyes), average value of tear break-up time (seconds; twice on both eyes), basal salivary flow (ml/15 minutes), average value of stimulated parotid (both sides) salivary flow (ml/10 minutes), dry eyes (visual analogue scale (VAS), 0-10 points), feeling of sand in the eyes (VAS, 0-10 points) and dry mouth (VAS, 0-10 points). The primary endpoints were Schirmer test and stimulated parotid salivary flow: an increase ≥25% was considered clinically significant.
The following laboratory parameters were assessed: ESR (mm/first hour), haemoglobin (mmol/l), serum IgA (0.5-3.7), IgG (8-17), IgM (0.4-2.3; g/l; turbidimetric method), IgA-Rf and IgM-Rf (IU/ml; as described previously)[18] and β_2-microglobulin (normal value <1.9 mg/l; radioimmunoassay, Pharmacia). All these laboratory measurements were performed serially from stored samples except for the ESR and haemoglobin.

STATISTICS

Spearman's rank-sum test was calculated for detecting a possible correlation between the different baseline study parameters. For comparison of groups, chi-square analysis was applied for discrete variables and Kruskal-Wallis ANOVA analysis for continuous variables. Changes of variables after intervention were evaluated with Wilcoxon's test for paired observations. A p value of ≤0.05 was considered significant.

RESULTS

Nineteen patients fulfilling the criteria for primary Sjögren's syndrome[17] were initially included. In *table 1* data are given on basic characteristics of these 19 subjects. Four patients had to stop with D-pen (250 mg/day) within three months, three because of severe loss of taste and one because of severe dermatitis and cheilitis. All these side effects were completely reversible after stopping the study medication. Fifteen patients completed at least three months treatment. These 15 patients are discussed in further detail. The group of 15 'completers' did not differ from the four 'non-completers' with respect to the characteristics from *table 1* except for a higher frequency of extraglandular symptoms in the last group ($p<0.05$). During the next three months, following increase of the dosage to 500 mg/day, three other patients had to stop D-pen because of severe side effects due to severe loss of taste, nausea and anorexia, and malaise and diplopia, respectively. All these side

Table 1

Characteristics (mean, range) of the 19 initially included patients with primary Sjögren's syndrome[17]

Age (years)	62.4 (34-79)
Sex (male/female)	4/15
Duration of established disease (years)	3.8 (0.5-11)
Anti-SSA and/or anti-SSB	12
Parotitis, past or present	4
Extraglandular manifestations*	6
Focus score ≥1 on minor salivary gland biopsy	12 (out of 16)

* *Polyneuropathy (2), cutaneous vasculitis in the past (1), optic neuritis in the past (1), distal renal tubular acidosis and encephalopathy possibly due to Sjögren's syndrome (1).*

effects were reversible after the study medication had been stopped. In one other patient the protocol was violated after three months as prednisolone had to be given because of severe polyarthritis. So, 11 patients were evaluable at six months. Two of these 11 patients experienced a mild cutaneous reaction not necessitating D-pen withdrawal. Thus, nine (47%) of the 19 patients included initially experienced side effects, leading to stopping the D-pen treatment in seven cases (41%). Neither haematological side effects nor significant proteinuria were seen.
At baseline, seven out of the 15 subjects had positive IgA-Rf levels (>5 IU/ml) while 11 had positive IgM-Rf levels (>10 IU/ml). In *table 2* data are given on clinical parameters prior to and after D-pen treatment. There was a significant increase in basal salivary flow after three months. Although values of both basal salivary and stimulated parotid salivary flow at three and six months were higher compared with baseline values, the differences were not statistically significant. There were no subjective improvements as recorded by VAS. With respect to laboratory parameters (*table 3*) we found significant reductions of ESR and levels of IgM-Rf and IgA-Rf. Reductions in levels of IgM-Rf and IgA-Rf were impressive. Levels of IgG also decreased but this was not statistically significant.

DISCUSSION

Up to now results of treatment of primary Sjögren's syndrome (PSS) with respect to the function of lacrimal and salivary glands are very disappointing. Experience with D-pen treatment in PSS is scarce though, theoretically, this agent might be effective. We undertook the first prospective protocolised study on D-pen treatment in PSS. This open, uncontrolled study was intended to be a pilot study. There were relatively many dropouts, only 11 (58%) out of the 19 patients initially included completed the study. Side effects were frequently observed, especially severe (reversible) loss of taste. Possibly, PSS patients are more sensitive to loss of taste because of their lack of saliva. Side effects in PSS patients probably occur much more frequently compared with rheumatoid arthritis.
We found significant serological effects following D-pen treatment, including significant reductions in ESR and levels of IgA-Rf and IgM-Rf. Especially impressive were the reductions in the levels of IgM-Rf and IgA-Rf. However, clinical effects after D-pen were limited to only a statistically significant increase in basal salivary flow after three months. One could speculate whether the strong reduction in levels of IgM-Rf and IgA-Rf are causally related to the increase in basal salivary flow.

Table 2

Clinical parameters (mean ± SD) prior to and after three and six months of treatment with D-penicillamine in patients with primary Sjögren's syndrome

	D-PENICILLAMINE TREATMENT		
	PRIOR TO (N=15)	AFTER THREE MONTHS (N=15)	AFTER SIX MONTH (N=11)
Schirmer test (mm/5 min)	4.4 (± 4.4)	6.1 (± 1.6)	5.4 (± 1.9)
Tear break-up time (seconds)	3.6 (± 2.1)	4.4 (± 3.6)	3.7 (± 1.9)
Salivary flow			
- Baseline (ml/15 min)	1.8 (± 2.2)	2.7 (± 3.2)*	3.0 (± 3.8)
- After stimulation (ml/10 min)	4.0 (± 2.7)	4.1 (± 3.3)	5.2 (± 3.6)
Dry eyes#	5.0 (± 1.4)	4.0 (± 2.7)	2.5 (± 3.3)
Sand in the eyes feelings#	5.0 (± 1.4)	4.0 (± 2.7)	2.5 (± 3.4)
Dry mouth#	5.8 (± 1.6)	6.3 (± 2.0)	2.5 (± 3.3)

* *P=0.042 versus prior to treatment, # VAS (visual analogue scale) = severity of symptoms as scored on a scale from 0 (no symptoms) to 10 (most severe symptoms).*

Table 3
Laboratory parameters (mean ± SD) prior to and after three and six months treatment with D-penicillamine in patients with primary Sjögren's syndrome

	D-PENICILLAMINE TREATMENT		
	PRIOR TO (N=15)	AFTER THREE MONTHS (N=15)	AFTER SIX MONTHS (N=11)
ESR (mm/first hour)	23.7 ± 22.6	23.7 ± 20.8	21.5 ± 23.6*
Haemoglobin (mmol/l)	8.5 ± 0.8	8.6 ± 0.9	8.7 ± 1.0*
IgA (g/l)	2.5 ± 1.1	2.4 ± 1.0	2.2 ± 0.8#
IgG (g/l)	13.2 ± 3.9	13.3 ± 4.4	11.8 ± 3.3
IgM (g/l)	1.6 ± 1.8	1.3 ± 1.3*	0.8 ± 0.6#
IgA-Rf (IU/ml)	37.5 ± 64.7	25.7 ± 50.0*	10.5 ± 19.6
IgM-Rf (IU/ml)	27.4 ± 61.0	22.5 ± 55.4*	5.5 ± 7.4
β_2-microglobulin (mg/l)	2.5 ± 1.1	2.6 ± 1.1	3.0 ± 1.6

*ESR = erythrocyte sedimentation rate, Ig = immunoglobulin, Rf = rheumatoid factor, * p<0.05 versus prior to, # p<0.02 versus prior to.*

Indeed, it has been reported that levels of IgA-Rf are inversely related to stimulated parotid salivary flow.[15] The feeling of sand in the eyes and dry mouth as measured by VAS after six months seemed to improve although not statistically significantly.

The relationship between autoantibodies (including rheumatoid factors) observed in PSS and its disease manifestations such as xerostomia and xerophtalmia is far from clear. Rheumatoid factors and other immunoglobulins are produced locally in salivary glands in PSS.[13,14] In the past it has been reported that the synthesis of immunoglobulins in the salivary glands does not correlate with serum immunoglobulin levels.[19] Perhaps this is, partly, the explanation for the discrepancy between the relatively small clinical benefit and the strong serological effects of D-pen in PSS.

Our patients had established PSS for a mean of 3.8 years implicating (partly) irreversible destruction of gland tissue. Possibly, a stronger clinical response might be observed when PSS is treated at an earlier stage of the disease when there is more active inflammation.

Our results are largely comparable with the findings of Kruize *et al.*, who could not demonstrate any beneficial clinical effect after treatment of PSS with hydroxychloroquine.[1] They found a reduction in serum levels of IgG and IgM but not of the ESR, IgA and rheumatoid factors. Because of the high rate of side effects and the small clinical benefit, we cannot recommend D-pen as systemic treatment for patients with long-lasting PSS. However, it might be that D-pen is more beneficial in PSS patients with earlier disease. A prospective, double-blind, placebo-controlled trial might prove the potential role of D-pen in the treatment of early PSS.

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