CLINICAL RESEARCH

Natural course of penicillamine nephropathy: a long term study of 33 patients

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Abstract

To elucidate the natural course of the nephropathy associated with penicillamine and thereby facilitate its clinical management 33 patients with rheumatoid arthritis who developed proteinuria during treatment with oral penicillamine were studied in detail throughout their renal illness. Renal biopsies were performed, and creatinine clearance and proteinuria were measured serially for 74 months (range 16-148 months). Fourteen patients developed proteinuria within six months after the start of treatment and 27 within 12 months. When treatment was stopped the proteinuria reached a median peak of 4·2 g/24 h (range 0·3-15·0 g/24 h) at one month (range 0-7 months) before resolving spontaneously by six months (12 patients), 12 months (21), or 18 months (29). In all patients but one, who developed carcinoma of the renal pelvis, proteinuria resolved by 21 months and its median duration was eight months. The median first and last measurements of creatinine clearance showed no appreciable change (80 ml/min and 78 ml/min), and no patient died from or needed treatment for renal failure. The HLA-B8 or HLA-DR3 alloantigen, or both, were identified in 10 patients. Renal biopsy specimens showed membranous glomerulonephritis in 29 patients, minimal change nephropathy in two, and electron dense deposits in the mesangial regions in two.

In all the patients whose nephropathy was due solely to treatment with penicillamine the proteinuria resolved completely when the drug was withdrawn; renal function did not deteriorate, and corticosteroids were unnecessary.

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Introduction

Penicillamine has been accepted as an effective second line treatment for rheumatoid arthritis, but complications are common and include renal damage in 5-30% of patients.[1-3] The renal damage presents as proteinuria of widely varying severity (0·3-20·0 g/24 h)[4-7] and the nephrotic syndrome in 16-70% of cases[3 4 7 8] and may cause this otherwise successful treatment to be stopped.[1] The peak incidence of proteinuria occurs in the second six months of treatment,[3-8] but it may develop at any time from six weeks to five years after treatment is started.[6 8] In some patients proteinuria resolves or falls below 0·5 g/24 h within 12 months after penicillamine is stopped,[4 5 8] but in others proteinuria in excess of 1 g/24 h persists[4 8 9]; no long term studies have been reported. The limited data available show that renal function at the time of renal biopsy is usually normal or only slightly impaired,[4 6] although serial and long term measurements have not been made. Recent immunogenetic studies showed that nephropathy associated with penicillamine is more likely to occur in patients with rheumatoid arthritis who are positive for the histocompatibility alloantigen HLA-B8 or HLA-DR3.[10 11] Renal biopsy has usually, but not invariably, shown membranous glomerulonephritis[1 4 9]; in patients with persisting proteinuria biopsies performed 12 months or more after treatment was stopped showed extensive immune deposits,[4 8] causing concern that progressive renal disease might develop.[1 4]

Current knowledge of penicillamine nephropathy is based on reports on small series of patients, which have yielded variable, incomplete, short term, and sometimes conflicting data. These data have led to appreciable variations in clinical practice: some clinicians stop giving penicillamine as soon as low grade proteinuria (>0·3 g/24 h) is detected,[4] whereas others continue it despite proteinuria within the range seen in the nephrotic syndrome (>3 g/24 h).[3 12]

We studied 33 patients with rheumatoid arthritis who also had penicillamine nephropathy in detail throughout their renal illness to obtain the serial data that are essential to understand the natural course of nephropathy and to facilitate rational management.

Patients and methods

From August 1973 to October 1984, 33 patients (11 men and 22 women) with rheumatoid arthritis, who had not had proteinuria previously, were referred with proteinuria that had developed during treatment with oral penicillamine. All patients fulfilled the criteria of the American Rheumatism Association for the diagnosis of rheumatoid arthritis, and 27 had circulating IgM rheumatoid factor. From 1973 to 1976 penicillamine was given at a starting dose of 250 mg daily, being increased at monthly intervals by 250 mg daily to 1000 mg daily taken in divided doses. From 1977 onwards a flexible low dose regimen was used, starting at 125 mg daily and increasing gradually at monthly intervals until the lowest dose that was clinically effective was reached (often 375-500 mg daily), which was then continued.

At intervals of one to two months during treatment the patients' urine was tested for proteinuria with reagent strips (Labstix; Ames, United Kingdom). When appreciable proteinuria (>0·3 g/24 h) was detected the specialist in rheumatology decided whether to refer the patients to a nephrologist. Once patients had been referred penicillamine treatment was stopped, 24 hour urinary protein excretion and creatinine clearance were measured, and intravenous urography and percutaneous renal biopsy were carried out. The biopsy specimen was processed by conventional methods and examined by light microscopy, immunofluorescence, and electron microscopy. Causes of proteinuria other than penicillamine nephropathy (amyloidosis, vasculitis, systemic lupus erythematosus, and analgesic nephropathy) were excluded by histological examination of the biopsy specimen, immunological tests for antinuclear factor and binding of deoxyribonucleic acid, and intravenous urography. Each patient was followed up at intervals of one to three months until the proteinuria had resolved and at intervals of one to two years thereafter, when 24 hour creatinine clearance and proteinuria were measured.

The results are presented as medians, interquartile ranges (defined by the 25th and 75th centiles), and total ranges to indicate the wide dispersion and non-parametric distribution of the data.

Results

Table I shows details of the patients and their treatment. The renal biopsies were performed two months (interquartile range 1-4, total range 0·1-29·0 months) after the treatment was stopped.

Proteinuria—Table II shows that the time of onset of proteinuria varied from two months to 74 months after treatment with penicillamine was started. The peak incidence occurred from four to 11 months, when 25 patients presented. Overall, 14 patients had presented by six months and 27 by 12. The severity of the proteinuria varied greatly (0·3-15·0 g/24 h) and was not related to the duration of treatment, the dose of penicillamine, or the presence of the HLA-B8 or HLA-DR3 alloantigen. The median initial and maximum measurements of proteinuria were 3·7 g/24 h (interquartile range 1·6-7·3 g/24 h) and 4·2 g/24 h (1·8-7·7 g/24 h), respectively. In 15 patients the initial measurement was also the maximum recorded, whereas in the 18 others proteinuria increased for 0·1-7·0 months (median one, interquartile range 0·1-3·0 months) after penicillamine treatment had been stopped. In 20 patients the proteinuria was within the range seen in the nephrotic syndrome (median 7·3 g/24 h, interquartile range 5·0-9·0, range 3·2-15·0 g/24 h) and persisted for a median of three months (interquartile range 1-5, range 1-14 months). In all cases the nephrotic syndrome was controlled by a diet high in protein and low in salt and by treatment with diuretics. In all but one patient, who subsequently developed fatal carcinoma of the renal pelvis, the proteinuria resolved completely. The median duration of the proteinuria was eight months (interquartile range 5-15, range 1-21 months) and six, 12, and 18 months after pencillamine had been stopped the proteinuria had resolved in 12, 21, and 29 patients, respectively (table III).

TABLE I—*Clinical details of 33 patients with rheumatoid arthritis and penicillamine nephropathy*

	Median	Interquartile range	Total range
Rheumatoid factor (IU)	596	240-1280	64-2048
Age at onset of rheumatoid arthritis (years)	45	36-50	18-71
Time between diagnosis of rheumatoid arthritis and start of penicillamine treatment (months)	75	34-153	6-370
Time between start of penicillamine treatment and onset of proteinuria (months)	8	5-11	2-75
Dose of penicillamine at onset of proteinuria (mg/day)	625	438-1000	125-1250

TABLE II—*Time of onset of proteinuria in 33 patients with rheumatoid arthritis during treatment with penicillamine*

Months of treatment	No of patients developing proteinuria	% Of patients	Cumulative %
1	0		
2	2	6	6
3	0		
4	1		
5	6	36	43
6	5		
7	1		
8	2	18	61
9	3		
10	3		
11	4	21	82
12	0		
16	1	3	85
18	1	3	88
20	1	3	91
40	1	3	94
46	1	3	97
74	1	3	100

TABLE III—*Resolution of proteinuria in 32 patients after penicillamine treatment stopped*

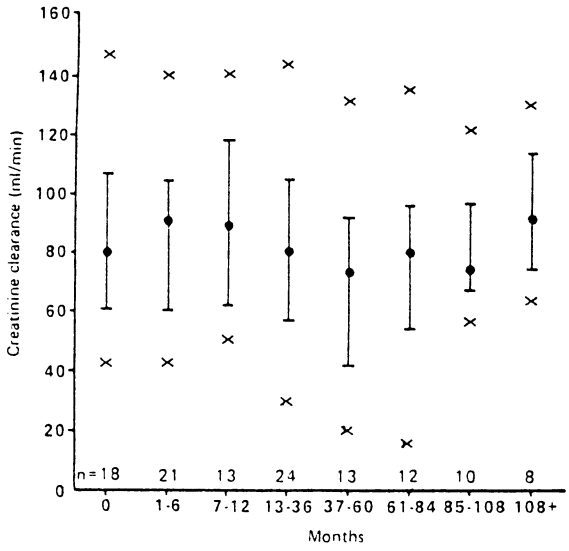
Months of treatment	No of patients with resolved proteinuria	Cumulative %
1	2	
2	4	16
3	5	
4	6	
5	10	38
6	12	
7	15	53
8	17	
10	18	
11	19	66
12	21	
13	23	
14	24	78
15	25	
17	26	91
18	29	
19	31	100
21	32	

Renal function—The median initial measurement of creatinine clearance was 80 ml/min (interquartile range 61-107, range 43-148 ml/min) and the latest 78 ml/min (interquartile range 62-106, range 16-148 ml/min) with an interval of 74 months (interquartile range 43-112, range 13-158 months). The figure shows the creatinine clearance measured in the first and second six month periods and within two year periods thereafter. In 13 patients creatinine clearances below 60 ml/min were recorded (median 43 ml/min, interquartile range 41-55, range 33-57 ml/min) five months (interquartile range 1-10 months, range 1-23 months) after penicillamine treatment had been stopped. In nine patients the creatinine clearance improved (median 72 ml/min, interquartile range 67-88, range 62-115 ml/min) and in two it remained stable (40 and 57 ml/min, respectively) during follow up. In two other patients renal function deteriorated (creatinine clearance fell from 42 to 20 ml/min over 40 months in one and from 38 to 16 ml/min over 74 months in the other) for reasons other than the effect of penicillamine, including rheumatoid vasculitis, malignant hypertension, and cardiac failure in the first and severe cardiac failure due to ischaemic heart disease in the second. No patient died of or needed treatment for chronic renal failure.

HLA typing—HLA-B8 was detected in 10 of the 18 patients whose tissue was typed, HLA-DR3 in eight, and HLA-DR4 in seven; 10 patients were positive for HLA-B8 or HLA-DR3, or both.

Renal ultrastructure—Adequate renal biopsy specimens were obtained from all patients. In 29 specimens ultrastructural changes characteristic of membranous glomerulonephritis were visible in the capillary loops with granular deposits of IgG and complement on immunofluorescence staining and subepithelial electron dense deposits were visible on electron microscopy. On light microscopy, however, epimembranous spikes were seen in only five specimens, proliferation of mesangial cells and matrix in 13, and no abnormalities in 16. The specimens from the remaining four patients showed proliferation of mesangial cells and matrix on light microscopy and no deposition of immunoglobulins and complement on immunofluorescence staining. Two of these specimens showed extensive fusion of the foot processes of the epithelial cells on electron microscopy, which, in the

absence of other important abnormalities, was compatible with minimal change nephropathy; the remaining two biopsy specimens showed electron dense deposits in the mesangial cells, indicating mesangial glomerulonephritis.



Creatinine clearance after penicillamine treatment stopped. (Numbers of patients in parentheses.) •=Median. x=Limit of range. Vertical bar=interquartile range.

Discussion

In this long term study we identified the clinical features that make up the natural course of penicillamine nephropathy. This condition occurs in patients of all ages and either sex with rheumatoid arthritis. Although proteinuria may occur at any time during treatment, 80% of our patients presented during the first 12 months and the median duration of treatment at the onset of proteinuria was eight months, confirming previous reports.[4-8] The suggestion that proteinuria is uncommon during the first six months of penicillamine treatment[3] was, however, not confirmed as we observed a high incidence in both the fifth and sixth months of treatment. Previous reports suggested that the incidence of proteinuria may be reduced by a low dose regimen (125-500 mg daily)[3 13 14]; we found that the incidence of proteinuria was appreciable even with such regimens as eight of our patients were receiving 125-375 mg daily and eight 500 mg daily. No clinical variables have been found that predict the development of nephropathy[1]; the reported association with HLA-B8 and HLA-DR3 is only partial and tissue typing is too complex and expensive for routine use.[10 11] Thus regular testing of urine with a reagent strip during treatment with penicillamine remains the best clinical test for detecting nephropathy.

We have confirmed previous reports that the severity and duration of proteinuria vary greatly and that there is no correlation with the dose of penicillamine or the duration of treatment.[4-7] Although in a few patients proteinuria increased for up to seven months after penicillamine was stopped, it peaked within three months in 82% of the patients and caused the nephrotic syndrome in 64% confirming previous reports.[4 8] There is general agreement that proteinuria gradually decreases when penicillamine treatment is stopped.[4 9] In three previous series in which patients were followed up for 12 months or longer, however, continuing proteinuria (0·4-1·7 g/24 h) was observed in 25-63% of cases and caused concern that a progressive renal lesion may develop in some cases.[4 8 9] We found that 40% of patients continued to have appreciable proteinuria (median 0·5 g/24 h, range 0·4-1·4 g/24 h) 12 months after stopping treatment. There was, however, no evidence of progressive renal disease as in all but one patient, who developed carcinoma of the renal pelvis, the proteinuria subsequently resolved completely.

Our data on creatinine clearance are the first long term serial measurements of renal function in penicillamine nephropathy and show that, except in the rare cases in which crescentic glomerulonephritis develops[15 16] (we did not see any such cases during the 10 years of the study), progressive renal impairment that can be attributed primarily to penicillamine nephropathy is extremely rare—if it occurs at all. In the two patients with severely impaired renal function that continued to deteriorate other important factors were present, including rheumatoid vasculitis, malignant phase hypertension, and refractory cardiac failure.

Our results show that in patients with proteinuria treatment with penicillamine should be stopped and renal function and proteinuria monitored at intervals of one to three months until the proteinuria has resolved. The nephrotic syndrome that develops in two thirds of those affected can be controlled with a diet high in protein and low in salt and by diuretics. Treatment with high doses of corticosteroids, which has been used previously,[17] is unnecessary and potentially hazardous, and there is no evidence that it shortens the duration of the proteinuria or leads to more rapid or more complete resolution of the renal lesion. Referral for renal biopsy is necessary only if proteinuria within the range indicating the nephrotic syndrome (>3 g/24 h) persists for more than one year; less severe proteinuria persists for more than two years; renal function deteriorates appreciably; or there is concern that a second disease (usually amyloidosis) may be present. In those uncommon cases of severe rheumatoid disease in which penicillamine is the only effective second line agent or the only such agent that the patient can tolerate treatment can probably be continued, as proposed previously,[3 12] provided that proteinuria and creatinine clearance are monitored carefully; it should be stopped immediately if severe proteinuria (>3 g/24 h) develops or renal function deteriorates.

Membranous glomerulonephritis, the renal lesion most commonly associated with penicillamine treatment,[4-9] was seen in 29 patients (88%) in the present series. Other renal lesions may occur, and we observed minimal change nephropathy in two patients and a mesangial immune complex lesion in two; some patients are reported to have developed proliferative glomerulonephritis with epithelial cell crescents[15 16] and IgA nephropathy (P R Harrison, A G MacIver, personal communication). Thus penicillamine nephropathy encompasses several types of renal damage due to different immunopathogenic mechanisms. In patients with rheumatoid arthritis who were not receiving penicillamine (or gold) treatment there was an increased incidence of both membranous glomerulonephritis and mesangial changes due to deposition of immune complexes in specific regions of the glomerulus.[1 18 19] Treatment with penicillamine may modify the immune system and alter polymeric proteins, enhancing the nephritogenic potential of existing rheumatoid immune complexes and thereby increasing the incidence of membranous glomerulonephritis and potentiating the mesangial lesion of rheumatoid arthritis.[1] Penicillamine is also a potent hapten[20] and as such may present antigens that are not primarily associated with rheumatoid disease—for example, the renal tubuloepithelial antigen and antigens of the glomerular basement membrane—to the immune system, leading to membranous glomerulonephritis and Goodpasture's syndrome, respectively.[1]

As treatment with penicillamine is effective and widely used for active and progressive rheumatoid disease nephropathy will continue to occur; detailed knowledge of the natural course of the condition is essential for its correct clinical management.

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Eye pain with nifedipine and disturbance of taste with captopril: a mutually controlled study showing a method of postmarketing surveillance

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Abstract

Several notifications of eye pain and blurred vision associated with treatment with nifedipine were received by New Zealand's Intensive Medicines Monitoring Programme. A questionnaire survey of patients taking nifedipine was undertaken to test the importance of these associations, with disturbance of taste associated with captopril taken as a methodological control. Altogether 961 patients taking nifedipine and 368 taking captopril were sent a questionnaire that asked whether any eye problems and changes in the sense of taste had occurred while they were taking the drug and whether these had resolved after treatment was stopped. Compliance was high: of 922 and 343 questionnaires that were assumed to have been delivered to patients taking nifedipine and captopril, respectively, 770 (84%) and 295 (86%) were returned satisfactorily completed. The distribution of sex was comparable in the two groups; patients taking captopril were slightly younger. Eye symptoms were reported in both groups, but eye pain was significantly more common in patients taking nifedipine (107 (14%) compared with 26 (9%) patients taking captopril). This is a new finding and may be related to ocular vasodilatation. Theoretically, glaucoma is a possible adverse reaction. Loss of taste was significantly associated with captopril, but no other disturbances of taste showed significant associations. Loss of taste persisted in 27 out of 35 patients who continued to take captopril and in three out of eight patients when the drug was withdrawn.

This study showed a method of assessing early signs of adverse drug reactions, which has been used once before and identified previously unrecognised reactions.

Introduction

Nifedipine was approved for marketing in New Zealand in October 1980 and placed in the Intensive Medicines Monitoring Programme.[1] In this programme the names and addresses of patients being treated with monitored drugs are sent to the Medicines Adverse Reactions Centre by dispensing pharmacists and held on computer file. Doctors prescribing such drugs are urged to report all adverse events experienced by their patients, and this spontaneous reporting is supplemented by surveys that try to complete the recording of all events. The two types of survey used are (*a*) surveys of reasons for stopping treatment and (*b*) surveys of the recording of events, in which doctors are asked to record all events noted in their patients' records while the patients are being treated with the monitored drug.

After the first two years of monitoring of nifedipine five records of eye problems had been received, three of painful eyes and two of blurred vision, and it was thought that the possibility of eye problems associated with nifedipine should be investigated. Disturbance of taste with captopril, a drug that was also being intensively monitored, is a known adverse reaction and was selected as a methodological control. Captopril was first marketed in April 1981.

Method

Questionnaires were posted to patients listed in both drug groups after consent was obtained from their doctors. The doctors were also able to advise of any deaths or provide other information about any inability to complete the questionnaires. Patients were asked for the following information. (1) Had treatment been stopped, and if so when? (2) Had their sense of taste changed and any eye problems developed since they started their treatment? (They were not told which drug was suspected of affecting the eyes or the sense of taste.) (3) If their sense of taste had changed they were asked to choose the best answer for the change from sweet, loss of taste, salty, metallic, and other; and for eye problems they selected from painful, stinging or dry eyes, and blurred vision. Some of these choices were included as a blind. (4) Had any of these symptoms caused them to stop taking the drug? (5) Had these symptoms cleared on withdrawal of the drug? (6) If symptoms were current they were asked to grade the severity in one of three categories: severe, moderate, or minor. (7) Did they smoke tobacco? Smoking could relate to taste and possibly eye problems. (8) Date of birth.

The questionnaire had been tested in a preliminary pilot study of about 100 patients; the only change had been the addition of the request for the date of birth. For patients taking nifedipine who said that they had experienced moderate or severe eye pain an ophthalmologist's opinion was requested through their general practitioner.

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