Leading article

D-penicillamine for primary biliary cirrhosis

In the mid 1970's an exciting new treatment for patients with primary biliary cirrhosis was proposed. The disease was by that time recognised as presenting not only with a picture of late 'obstructive' jaundice, but more often with non-specific symptoms, particularly pruritus, or malaise and abdominal pain.[1] Although the cause of primary biliary cirrhosis was not (and is not) understood, the hepatic deposition of copper was recognised and by analogy with Wilson's disease, the possible function of copper causing liver damage was postulated.[2] During the 1970's the role of immune complexes in the aetiology, or at least in the perpetuation of primary biliary cirrhosis, was proposed.[3]

D-penicillamine was clearly useful in patients with Wilson's disease,[4] and it was active in improving rheumatoid arthritis:[5] possibly by decreasing deposition of immune complexes and it had the added bonus of impairing the maturation of collagen,[6] thus possibly slowing progression towards cirrhosis. Thus by 'acting here, here and here' – to coin a phrase – it appeared to offer the hope of an effective treatment for primary biliary cirrhosis. Accordingly between 1975 and 1979 at least seven controlled trials were set up in Europe and the United States. The hope of success was enhanced by preliminary reports[7] of decreased immune complexes and immunoglobulins and removal of copper by D-penicillamine from the liver.[8]

Unfortunately what appeared so straightforward and hopeful has not been confirmed. Recent studies of the natural history of the disease[9][10] suggest that three broad groups of patients can be considered. There is a pool of asymptomatic (or almost asymptomatic) patients, most with an early histological stage of the disease, but some with established cirrhosis. These individuals have a normal, or near normal life expectancy. There are still a number of patients who present for the first time with jaundice and signs or symptoms of liver failure, or portal hypertension; the prognosis in this group is poor. There is also an intermediate group, usually detected because of pruritus, malaise, or non-specific symptoms. The exact size of this group in relation to the whole is debatable, as is their prognosis, but it probably represents 50–70% of all patients, with a life expectancy of perhaps 5–10 years from diagnosis in most of these individuals.

Understanding of the pathogenesis of primary biliary cirrhosis is still poor. While hepatic deposition of copper is progressive and correlates with the stage of the disease, its pattern of hepatic retention is different from Wilson's disease and it is probably not important in pathogenesis.[11] Likewise although immune complexes circulate in the serum of patients with primary biliary cirrhosis, this may well be another epiphenomenon,

rather than an important pathological·mechanism.[12]

In 1981 the preliminary results of treatment with D-penicillamine of 87 patients for a mean period of 44 months in a controlled trial showed better survival in the treated group and also possible histological and biochemical improvement.[13] These observations were supported by those of the Mayo Clinic group in 1982.[14] This initial optimism has not, however, been confirmed either by further follow up and expansion of the studies cited or by the well-conducted European multicentre trial reported in this issue of *Gut*.[15] A summary of the major reported controlled trials is in the Table.[15–21] Although it is disappointing that seven controlled trials involving 767 patients have not shown improved survival on D-penicillamine treatment of primary biliary cirrhosis, a number of lessons may be drawn. These may be categorised as direct lessons and as being wise after the event.

The main direct lesson is that, as in rheumatoid arthritis, D-penicillamine causes adverse reactions, severe enough for the treatment to be discontinued in about one third of the patients. Although only one death was attributed directly to the therapy, thrombocytopaenia, proteinuria, lichen planus and other rashes, and LE-like illness and a severe myasthenic syndrome were all recorded. A second conclusion is that if D-penicillamine treatment is beneficial, then the effect is almost certainly small. Wiesner *et al* concluded after a controlled trial in 310 patients that 'the data are statistically inconsistent with the hypothesis that D-penicillamine provides at least a 50% improvement in survival over placebo'.[17] Nonetheless in the multicentre trial reported in this issue, the mortality rate in early stages of the disease among the treated group was one third of that seen in the placebo treated patients (p=0·15).

Lessons which we may call being wise after the event relate to increased understanding of the natural history of the disease and to improved comprehension (at least among some of the investigators) of the implications of this clinical spectrum on the design of trials. It has become clear that until more is known of the cause, or causes of primary biliary cirrhosis there is little justification for treatment of asymptomatic patients, particularly with early histological lesions, because their life expectancy is excellent and the 'cure' may·be worse than the illness. On the other hand it now appears unlikely that any treatment which we can at present envisage, apart from liver transplantation, will benefit primary biliary cirrhosis patients with marked jaundice and established signs of hepatic decompensation – in short with end-stage liver disease. Thus any new treatment should be particularly aimed at the intermediate group of patients – those with some symptoms, but not clinically and histologically at 'end stage'. This intermediate group probably accounted for only 50–70% of patients entered into the D-penicillamine trials, thus diluting treatment and placebo groups with some individuals who were destined to die regardless of treatment, and with a larger number in whom active therapy could not be expected to show improved survival, because they were destined to survive anyway. Realisation of this has led to an examination of the design and interpretation of the published trials. Epstein and colleagues calculated the number of patients necessary to determine reduction in five year mortality from 40–30%, with 80% certainty at 5% significance.[16] They suggested that a controlled trial

Table   Controlled trials of D-penicillamine treatment for primary biliary cirrhosis

Trial	Patients (no)	Mean follow up	D-P dose (mg/day)	Adverse reactions	Results of treatment			
					Liver function/histology		Mortality	
					Interim	Latest	Interim	Latest
European Multicentre[15]	189	c.24	1200	36% treated pts withdrawn	Histological improvement ↓AST, immunoglobulins, copper	No benefit	Reduced (p<0.01) after 45/12	No statistical benefit
Royal Free Hospital[13 16]	98	66	600	c.1/3 withdrawn		No benefit		No statistical benefit (p=0.08)
Mayo Clinic[14 17]	310	NS*	1000	105 in 155 patients	↓AST, alk phos, immunoglobulins, copper	No histological benefit	Reduced	No benefit
Boston[18]	52	28	1000	'major' 31%	↓AST, copper			No benefit
Newcastle[19]	59	36	250 or 1000	'severe' 37.5%	↓AST, alk phos, immunoglobulins			No benefit
Sheffield[20]	35	c.24	875	1 patient withdrawn	Histological improvement			No benefit
Holland[21]	24	NS	1000	2/11 treated pts withdrawn	↓Immunoglobulins, copper			No benefit

* Total study 9 years

involving 710 patients would be necessary – ironically, a number not dissimilar from the total number of patients enrolled into the published trials. It is further suggested that a definite end point in time should be decided before the trial begins, because timing of analysis may otherwise be determined by the trialists during the course of such a long study according to previous criteria.

In a disease with an often leisurely natural history, other variables besides mortality should be examined. Neuberger and colleagues provide persuasive arguments elsewhere in this issue that the best method for analysis of clinical, serological, and histological features is by life table analysis, using the log rank test for comparison of groups.[22] This allows for incomplete follow up due to death, withdrawal, or drop outs. By using the occurrence rate ratio to analyse the effect of treatment, they claim a more effective discrimination of the population trend, than by measuring the percentage changes of clinical and biochemical variables with time.

The verdict on D-penicillamine treatment for primary biliary cirrhosis is the Scottish one of 'case not proven'. The likelihood is that there is a marginal decrease in mortality in the middle, symptomatic, group of patients, but the price of adverse reactions to the drug is probably too high to justify the further long and elaborate clinical trials necessary to prove the point, particularly when other treatments now under consideration – notably cyclosporin and prednisolone – may offer better results.

In future testing of new treatments for primary biliary cirrhosis it seems that simple controlled trials, even with stratification of patients, may not be enough. Careful thought should be given to the size of the population to be studied to ensure that the trial is powerful enough to indicate the efficacy of the treatment. The objects of each study should also be clearly understood – is mortality alone the criterion of success or failure, or will clinical, histological, and biochemical measurements also be examined by such useful statistical tools as occurrence rate ratio and life table analysis? Attention must also be paid to the group or groups of patients studied – asymptomatic, symptomatic, or late. In this way the inconclusive results reported after almost a decade of effort with D-penicillamine may not be repeated with new drugs.

O F W JAMES

Freeman Hospital,
Newcastle-upon-Tyne

References

1 Sherlock S, Scheuer PJ. The presentation and diagnosis of 100 patients with primary biliary cirrhosis. *N Engl J Med* 1973; **289:** 674–8.
2 Fleming CR, Dickson ER, Baggenstoss AH, McCall JT. Copper and primary biliary cirrhosis. *Gastroenterology* 1974; **67:** 1182–7.
3 Wands JR, Dienstag JL, Bhan AK, Feller ER, Isselbacher KJ. Circulating immune complexes and complement activation in primary biliary cirrhosis. *N Engl J Med* 1978; **298:** 233–7.
4 Walshe JM. Treatment of Wilson's disease with pencilllamine. *Lancet* 1960; **1:** 188–91.

5 Multicentre Trial Group. Controlled trial of D-penicillamine in severe rheumatoid arthritis: double blind controlled study of a high and low dose regimen. *Ann Rheum Dis* 1975; **34:** 416–21.
6 Deshmukh K, Nimni ME. A defect in the intramolecular and intermolecular cross linking of collagen caused by penicillamine. *J Biol Chem* 1969; **244:** 1787–95.
7 Epstein O, De Villiers D, Jain S, Potter BJ, Thomas HC, Sherlock S. Reduction of immune complexes and immunoglobulins induced by D-penicillamine in primary biliary cirrhosis. *N Engl J Med* 1979; **300:** 274–8.
8 Deering TB, Dickson ER, Fleming CR, Geall MG, McCall JT, Baggenstoss AH. Effect of D-penicillamine on copper retention in patients with primary biliary cirrhosis. *Gastroenterology* 1977; **72:** 1208–12.
9 James OFW, Macklon AF, Watson AJ. Primary biliary cirrhosis: a revised clinical spectrum. *Lancet* 1981; **1:** 1278–81.
10 Roll J, Boyer JL, Barry D, Klatskin G. The prognostic importance of clinical and histological features in asymptomatic and symptomatic primary biliary cirrhosis. *N Engl J Med* 1983; **308:** 1–7.
11 Epstein O, Arborgh B, Sagiv M *et al.* Is copper hepatotoxic in primary biliary cirrhosis? *J Clin Pathol* 1981; **34:** 1071–5.
12 Goldberg H, Kaplan MM, Mitamuri T *et al.* Evidence against an immune complex pathogenesis of primary biliary cirrhosis. *Gastroenterology* 1982; **82:** 677–83.
13 Epstein O, Jain S, Lee RG *et al.* D-penicillamine treatment improves survival in primary biliary cirrhosis. *Lancet* 1981; **1:** 1275–7.
14 Dickson ER, Wiesner RH, Baldus WP, Fleming CR, Ludwig JL. D-penicillamine improves survival and retards histologic progression in primary biliary cirrhosis. *Gastroenterology* 1982; **82:** 1225.
15 Neuberger J, Portmann B, Caballeria J *et al.* Double-blind controlled trial of D-penicillamine in patients with primary biliary cirrhosis. *Gut* 1985; **26:** 114–9.
16 Epstein O, Cook DG, Jain S, Sherlock S. D-penicillamine in PBC – An untested (untestable?) treatment. *J Hepatol* 1985; **1:** S49.
17 Dickson ER, Wiesner RH, Baldus WP *et al.* D-penicillamine trial for primary biliary cirrhosis. *Gastroenterology* 1984; **86:** 1062.
18 Matloff DS, Alpert E, Resnick RH, Kaplan MM. A prospective trial of D-penicillamine in primary biliary cirrhosis. *N Engl J Med* 1982; **306:** 319–26.
19 Bassendine MF, Macklon AF, Mulcahy R, James OFW. Controlled trial of high and low dose D-penicillamine in primary biliary cirrhosis. [Abstract] *Gut* 1982; **23:** A909.
20 Triger D, Manifold IH, Cloke P, Underwood JCB. D-penicillamine in primary biliary cirrhosis: two year results. [Abstract] *Gut* 1980; **21:** A919–20.
21 Taal BG, Schalm SW, Tenkate FW, Van Berge Henegouwen GP, Brandt KH. Low therapeutic value of D-penicillamine in a short-term prospective trial in primary biliary cirrhosis. *Liver* 1983; **3:** 345–52.
22 Peto R, Pike MC, Armitage P *et al.* Design and analysis of randomised clinical trial requiring prolonged observation of each patient. II Analysis and example. *Br J Cancer* 1977; **35:** 1–39.