Annotation

**D-penicillamine in rheumatoid arthritis**

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D-penicillamine (D-pen) has gained widespread use as a potent suppressor of disease activity in rheumatoid arthritis (RA) and juvenile chronic arthritis (JCA). The drug has been established for antirheumatoid therapy on the basis of a considerable number of comparative clinical studies of D-pen treatment versus placebo or other disease modifying antirheumatic drugs (DMARDs). Despite the positive outcome of these trials, no comprehensive understanding of its mode of action has emerged. Development of more differentiated drug strategies, construction of combination treatment protocols and generation of agents with defined target specificities may imply a more favourable benefit to risk ratio in the management of RA.

Key words: D-penicillamine; rheumatoid arthritis.

D-penicillamine (D-pen) belongs to the class of disease modifying antirheumatic drugs (DMARDs) capable to induce clinical and serological remission in rheumatoid arthritis (RA) over a period of months. D-pen (dimethylcysteine) was first discovered in the acid hydrolysate of penicillin by Abraham et al in 1943. Systemic D-pen treatment was introduced for RA because of its ability to dissociate rheumatoid factor in vitro and in vivo by reducing disulfide linkages. Although this is no longer a tenable explanation to its antirheumatoid potential, subsequent clinical trials have definitely established D-pen as a remittive agent in seropositive and seronegative rheumatoid arthritis as well as in juvenile chronic arthritis.

D-pen exerts a variety of biological effects of possible but as yet unproven relevance to its application in RA. These effects include interference with macrophage function by promoting phagocytosis, inhibition or enhancement of lymphocyte activation by mitogens, suppression or immunoglobulin synthesis, reduction of circulating alpha-1 antitrypsin-IgA complexes, stimulation or suppression of prostaglandin synthesis, inhibition of polio virus replication, antagonism with vitamin B6, heavy metal chelation and inhibition of collagen biosynthesis and crosslinking. Many of these effects can be explained in terms of the chemical structure of the drug.
Rheumatoid synovitis follows a biphasic course. The first, exudative phase is characterized by increased vascular permeability elicited by inflammatory mediators, e.g. kinins, complement components and prostaglandins. The second, granulomatous phase arises through complex interactions between committed macrophages and lymphocyte subpopulations. The mesenchymal effector cells are then activated by the release of cell factors, e.g. interleukins to produce excessive proportions of inflammatory connective tissue and matrix degrading enzymes. The etiology behind the sustained inflammatory activity remains obscure although microbial (viruses, mycoplasmas) and autoimmune mechanisms (type II collagen) have been implicated.

The spontaneous course of RA includes exacerbations and remissions that occur for unknown reasons. Therefore, clinical trials on antirheumatoid drugs must be conducted under carefully controlled conditions. The proper design of such studies implies prospective, double-blind comparisons with placebo or other established therapeutic modalities in well characterized groups of patients. The first study of this kind on D-pen was published by the Multicentre Trial Group in 1973. In this setting D-pen at 1.5 gm daily for 12 months was superior to placebo as regards pain score, morning stiffness, grip strength, Richie index, functional class, ESR and Hb. Between 1975 and 1977 four additional placebo controlled studies using doses a 0.6-1.2 g per day confirmed the antirheumatoid potency of D-pen. Studies comparing D-pen within the same dose range with myocrisin, levamisole and azathioprine have revealed no differences with respect to disease suppression between these drugs. Generally, however, the withdrawal rate increases with the duration of the therapy, amounting to 50-70% after more than one year treatment. The main reasons for cessation of the therapy are adverse reactions, disease exacerbation or therapeutic failure.

In contrast to adult RA, only few reports have been published on the effect of D-pen in juvenile chronic arthritis (JCA). Schairer reported an uncontrolled, retrospective study comprising 235 JCA patients treated with D-pen at 10-30 mg/kg/day. Improvement occurred in 77% over a period of one month to four years. In another uncontrolled trial by Ansell, D-pen within the dose range 10-30 mg/kg/day was used for seropositive and seronegative JCA. Patients benefited from D-pen as first disease modifying drug were 69%, and 53% had experienced therapeutic failure with other agents. Clinical improvement was accompanied by radiological healing of erosions. Recently two randomized, controlled studies have been published comparing D-pen with placebo and hydroxychloroquine or gold sodium thiomalate respectively. The first study is a multicentre comparative, double-blind study of the efficacy of D-pen versus placebo. D-pen 5-10 mg/kg/day for six months was superior to placebo as reflected by decreased number of stiff and painful joints and diminution of concomitant non-steroidal anti-inflammatory drug consumption. In the second trial by Kviens et al, D-pen at 2, 5-10 mg/kg/day for approximately one year was compared to hydroxychloroquine and gold thiomalate in pauci- and polyarticular JCA. The three drugs had similar abilities to modify the disease activity in these categories of the disease.