Leading Article

Colchicine – expanding horizons

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To say that the once very limited indications for colchicine have undergone a subtle but definite and dramatic change in recent years would not be an overstatement. This old drug, which has been known for centuries, was used for relieving and preventing acute attacks of gouty arthritis for over 200 years, but until recently, no other clinical uses had been established. The 1985 edition of Goodman & Gilman's standard textbook of pharmacology for example, states that '... colchicine is largely effective only against gouty arthritis', and devotes no more than five lines (of the two pages discussing the drug) to its possible effect in other conditions.¹ However, intriguing data have been obtained since, which suggests that colchicine may be highly efficacious in several common and important though diverse clinical syndromes for which no other equally effective therapy is known.

In gouty arthritis, its classical indication, the role of colchicine has been recently questioned since serious toxicity may be associated with its use, and since other agents such as indomethacin are as effective, and may be better tolerated.^{2,3} However, long experience has shown that the drug is remarkably well tolerated,⁴ and that cases of severe systemic toxicity are rare and often reflect inappropriate use of the drug⁵ (intravenous administration which exceeded 4 mg for a single course of therapy). The most common adverse effects of colchicine are relatively minor gastrointestinal symptoms, which are useful early signs of impending toxicity. Colchicine produces a striking response in acute gout where 0.5 mg is usually given orally, every 1–2 hours to a maximum of 8–10 mg, until relief or gastrointestinal symptoms occur. Pain and swelling usually abate within 12 hours of starting therapy and a major objective improvement of joint inflammation is evident within 48 hours and can be used as a diagnostic aid. The drug reduces the inflammatory reaction to urate crystals

without causing analgesia or affecting uric acid metabolism.⁶ Colchicine is also highly efficacious for the long-term prophylaxis of recurrent gout and the prevention of acute attacks during the first few months of treatment with allopurinol or uricosurics.⁴ One to two mg/day of colchicine may also be effective for prophylaxis of pseudo-gout⁷ and treatment of sarcoid arthropathy,⁸ psoriatic arthritis,⁹ and Paget's disease of bone,¹⁰ though at present the amount of information is inadequate for definite conclusions.

In recent years, however, additional indications for the use of colchicine have been identified, for which no known alternative exists. Best established so far is the role of colchicine in familial Mediterranean fever (FMF), an acute recurrent polyserositis of unknown aetiology affecting primarily Sephardic Jews and Armenians and leading to renal AA amyloid deposition with progressive proteinuria and renal failure. Daily administration of colchicine (1 to 2 mg), which appears to be well tolerated and safe in large numbers of patients of all ages, not only prevented or markedly ameliorated the acute painfully disabling feeble attacks in over 90% of FMF patients,¹¹ but was also able to prevent the development of amyloidosis or halt its progression in patients who were already affected.¹² This conclusion is not based on a double-blind study, yet the comparison with noncompliant patients and those studied before colchicine was used, the large numbers of patients and the long-term follow-up, make the results highly credible. Among FMF patients without overt renal disease only 4/906 developed proteinuria, as opposed to 16 of the 54 noncompliant patients (about 30%). The effectiveness of colchicine is more limited in patients who already have clinical amyloidosis; however, most of the patients who were proteinuric when treatment was commenced (but with no nephrotic syndrome or uraemia), remained in stable condition.¹² These effects of colchicine, which have already improved both the quality of life and survival in thousands of FMF patients, are based on observations *in vitro* (colchicine inhibits the secretion of serum amyloid A protein, an acute phase reactant synthesized by hepatocytes which is

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the precursor of AA amyloid) and in experimental animals.^{13,14} Thus, the beneficial effects of colchicine may extend to AA amyloidosis complicating other inflammatory diseases such as ulcerative colitis,¹⁵ and colchicine is also frequently administered to patients with immunoglobulin type (AL) amyloidosis. In this disease, colchicine improves median survival (according to an open trial based on comparison with historical controls),¹⁶ and can be highly beneficial in selected cases.¹⁷ A randomized study and several case reports suggest that it may be more effective in conjunction with melphalan/prednisone.^{18–20} The mechanism of the anti-amyloid effect of colchicine remains unclear, but, interestingly, it appears to be independent of the suppression of attacks or of the suppression of SAA secretion.^{12,21} The effect of colchicine in FMF has been mainly linked to its anti-inflammatory activities which are discussed below.

No less intriguing are the accumulating data on the possible effects of colchicine in immune-mediated disorders. Several uncontrolled studies and case reports suggest that patients with Behçet's syndrome may show a 60–70% response rate to colchicine.^{22,23} Oro-genital and ocular lesions seem to respond best, but the drug may also be effective for the associated articular and cutaneous manifestations and in prophylaxis. Controlled trials of colchicine in Behçet's syndrome are few and have not demonstrated unequivocal effect.²⁴ Leukocytoclastic vasculitis may also be amenable to colchicine therapy.^{25–27}

The basis for the use of colchicine in these conditions is its effects on polymorphonuclear leucocytes (PMNL), but mononuclear cells are also affected. By binding to a microtubular protein and other mechanisms which are incompletely understood, colchicine interferes with many basic cellular functions, including mitosis and PMNL-chemotaxis and adhesiveness. It also increases leucocyte cAMP levels, thereby inhibiting lysosomal degranulation and enhances release of prostaglandin E which suppresses leucocyte functions.²⁸ In addition to its antimitotic and anti-inflammatory effects, colchicine impairs collagen synthesis and enhances collagenase activity – an antifibrotic effect.²⁹ More recently, important inhibitory effects on cell-mediated immune responses have been noticed. These include inhibition of immunoglobulin secretion, interleukin-1 production, histamine release and interferon-induced expression of HLA-DR.^{30–32}

Though most of these observations have been obtained *in vitro*, a therapeutic value for colchicine has been demonstrated in at least two animal models of autoimmune diseases. Colchicine reduced proteinuria in passive Heymann nephritis in rats, an analogue of membranous glomeruloneph-

ritis in humans.³³ The drug can effectively prevent the development of clinical signs and histological lesions of acute experimental allergic encephalomyelitis in mice, an analogue of multiple sclerosis,³⁴ possibly by interrupting effector responses to myelin basic protein-primed T cells.

The growing understanding of the pleiotropic actions of colchicine and the realization of the important interactions between lymphoid components and fibroblasts at inflammatory sites which produce a vicious cycle of inflammation and fibrosis³⁵ have led to trials of colchicine in two human autoimmune diseases in which there is prominent and contiguous fibrosis and inflammation, in the absence of any effective therapy. In progressive systemic sclerosis and localized scleroderma, long-term colchicine therapy was claimed to be beneficial to most patients, especially when the duration of the disease was less than 5 years.³⁶ More accurate data are available in primary biliary cirrhosis, where colchicine was compared with placebo in two large double-blind controlled trials. Although there was no histological improvement over 2–5 years, patients at all stages who received colchicine (0.6 mg twice daily) had significant improvement or stabilization in liver function tests as compared to the placebo group, and mortality was also decreased by half.^{37,38} Colchicine has also been tried in cirrhosis with no autoimmune features (alcoholic or postnecrotic cirrhosis) and the results have also been potentially exciting affording a measure of hope for yet another large group of patients whose 5 year survival once the complications of cirrhosis develop is below 20%, and for whom effective therapeutic approaches are scarce. In a 14 year double-blind, placebo controlled trial of colchicine (1 mg per day, 5 days per week) in 100 cirrhotic patients in Mexico, a striking improvement in median survival was found in the treatment group (from 3.5 to 11 years), with significant reduction in deaths from liver failure and a possible improvement in liver histology.³¹ Though these results are open to several criticisms,³⁹ they are nevertheless highly encouraging and supported by an effect of colchicine in the treatment of experimental cirrhosis in animals^{40,41} and by the findings of other groups.⁴² Overall, colchicine was well tolerated and the drug's 'Excellent Safety Profile' was noted by investigators in many different studies.

There are numerous other anecdotal reports suggesting the usefulness of colchicine in diseases such as refractory idiopathic thrombocytopenic purpura, relapsing polychondritis, sclerosing cholangitis, recurrent aphthous stomatitis, dermatitis herpetiformis, and recurrent pericarditis (idiopathic or systemic lupus erythematosus-related).^{43–48} In some cases a rapid and 'spectacular'

response was observed and a possible effect of colchicine in prophylaxis of these immune-mediated disorders^{44,48} should be evaluated. Efficacy of colchicine has also been suggested in the prevention and treatment of abdominal pains in patients with hepatic porphyria.⁴⁹ However, all these results should be interpreted with caution since the treatment was uncontrolled and has been tried in very few patients so far.

Lessons from animal models indicate that colchicine may be utilized to advantage in several other situations of great clinical significance. Pre-treatment with colchicine protected the liver of rats against carbon tetrachloride or D-galactosamine-induced toxicity, possibly by acting as a free radical scavenger and by inhibiting drug-induced lipid peroxidation.^{50–52} Its possible value in human toxic hepatitis remains to be determined (prevention of halothane hepatitis?), though one trial of colchicine in alcoholic hepatitis showed no effect.⁵³ A significant inhibitory activity of colchicine on peritoneal adhesion formation or on proliferative vitreoretinopathy following abdominal or retinal surgery in experimental animals was also found,^{54,55} but no comparable human studies have been reported so far. Paraquat-induced lung injury appears to be related mainly to free radical-mediated lipid peroxidation and to a stage of excessive collagen synthesis that follows. As the

models discussed above suggest, colchicine may inhibit both mechanisms suggesting a possible efficacy in a model of paraquat lung damage in rats.⁵⁶

Colchicine confers the dual advantages of being both an inexpensive and a usually safe and well tolerated drug, despite its pleiotropic activities. However, adverse effects may occur and should be recognized. The most frequent are those involving the gastrointestinal tract which may be associated with the antimitotic action of colchicine. Often, diarrhoea, nausea, vomiting and abdominal pain are the first signs of toxicity and indicate that colchicine therapy should be stopped, or the dosage reduced. Other adverse effects include cytopenias, myoneuropathy (particularly in patients with altered renal function), rashes, alopecia and incidental cases of decreased sperm count or function have also been described.^{1,22,57} Thus, care should be exercised if treating patients at special risk (e.g. pregnancy, reduced renal function) and a periodic monitoring of patients undergoing prolonged colchicine treatment is recommended,²⁶ especially when renal or hepatic dysfunction exist.⁵ However, the overall safety record of the drug in large and diverse groups of patients is remarkable, and further controlled studies will probably establish its use in several important diseases, either alone or as an adjunctive treatment.

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