Editorial Comment

Old Drugs With New Uses
Colchicine for Treatment of Recurrent Pericarditis

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Drugs with a long history of efficacy for muscular aches and pains and inflammatory joint disease are being given new applications in the treatment of cardiovascular disease. The antiplatelet effect of aspirin has found a place in the prevention of coronary thrombosis. Now colchicine, an old friend in the treatment of gouty arthritis, may have found a new use in the management of recurrent pericarditis. In this issue of Circulation,1 Guindo and coworkers report on the relief of pericardial pain with colchicine in a small series of patients with recurrent pericarditis on usual medical management. This experience is important because all of the patients had pain relief while they took colchicine. Equally impressive is the ease with which patients could be withdrawn from adrenal corticosteroids without exacerbation of symptoms. These are remarkable results when the difficulties in treating symptomatic recurrent pericarditis are considered. One has to wonder why colchicine was ever considered as a possible therapy for recurrent pericarditis; perhaps it is because of its reported efficacy in the management of familial Mediterranean fever, a condition associated with polyserositis, including pericarditis.2,3

Recurrent pericarditis refers to repeat attacks in patients with no evidence of a systemic disease, that is, the pericarditis is idiopathic and presumably occurs as an autoimmune reaction. The condition is not common, but certainly not rare. Fowler and Harbin4 reviewed reported prevalence values for recurrent pericarditis of about 15–30% in larger series of patients with pericarditis of unknown cause. In general, the recurrences are few in number and respond to the usual treatment modalities applied to the first episodes of pericarditis, including hospitalization and symptomatic relief of pain with an anti-inflammatory agent such as aspirin, ibuprofen, or indomethacin and an analgesic such as morphine or Demerol. If pain or effusion continues, a corticosteroid, usually prednisone, is given. If the effusion increases and there is a threat of cardiac tamponade, pericardial drainage is undertaken. When a search for a specific etiology is negative during the initial episode and the evidence for pericarditis subsequently disappears, there is usually little need for further etiologic searches with recurrences.

With even later recurrences, there is rarely a need for hospitalization. Major complications, such as cardiac tamponade, constrictive pericarditis, and myocarditis, are rare with later attacks. However, in our experience, a well-trained cardiologist in practice is more likely to call a university medical center for advice on the management of recurrent pericarditis than for almost any other management problem. This clearly reflects the frustration of the physician as well as the patient when usual medical management fails and recurrences are frequent or prolonged. It is hoped that unusual expertise and newer but unreported therapies may be available. Unfortunately, the patient may by then have suffered complications from ever-increasing steroid doses. Pericardiectomy may have been performed with no relief of recurrent pericardial pain; the success rate for pericardiectomy varies from less than 50% to as much as 80%. We have used azathioprine in a few patients with no apparent benefit. Azathioprine therapy of steroid-responsive pericarditis was reported to be effective in 1970,5 but favorable reports by others have been conspicuously scarce.

In this context, the remarkable experience of Guindo and coworkers must be viewed with a mixture of, on the one hand, hope that their findings will be confirmed by others and, on the other hand, expectation that users will take a critical and scientific posture until the results of a larger study population are reported.

As cardiologists who deal with difficult management problems involving recurrent pericarditis in individual patients, we may elect to use colchicine when other therapies have failed. The authors recommend colchicine in the usual doses for chronic gouty arthritis, 1 mg/day; at this dosage, side effects should be minimal. However, the possible toxicity of long-term administration of colchicine is not well

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known. In addition to gastrointestinal symptoms with acute administration, azoospermia and chromosomal abnormalities have been reported with long-term therapy.6

The article by Guindo and coworkers does not represent a controlled, blinded, prospective study. A small series of patients was treated, and they served as their own controls. The period of symptom-free follow-up was sufficiently long compared with intervals between repetitive attacks before colchicine therapy for efficacy to be inferred in this small group of patients. The possibility exists that the prolonged symptom-free periods while on colchicine would have occurred anyway because the disease became dormant or burned itself out—hence the need for concurrent or historical controls. A definitive answer will require a large, double-blind, controlled, prospective, multicenter study, but it is unlikely, in my judgment, that such a study could be accomplished in a reasonable period of time at reasonable cost considering the uncommonness of the condition and the low likelihood that participating physicians would want to enter their patients as controls when a simple and probably safe therapy of unproven but suggestive efficacy is available.

Therefore, there is a need for historical controls who have been followed for long periods of time and suffered three, four, or five prior recurrences of known durations between attacks. Although there is a paucity of such studies in the literature, at least one natural history study is available.4 Fowler and Harbin reported a retrospective follow-up study of 31 patients with recurrent pericarditis; follow-up was 2–19 years. Twenty-four of the patients had idiopathic pericarditis, four had postoperative or post-traumatic pericarditis, two had postinfarction pericarditis, and one had pericarditis after anticoagulation-induced pericardial bleeding. None had evidence of systemic disease, and the cause of the recurrent pericarditis was considered to be an autoimmune mechanism. The frequency of remissions was not available, but duration of remissions was reported. Remissions were defined as symptom-free periods off medication that were followed by at least one subsequent attack. Remissions longer than 1 month were reported in 23 of the 31 patients. Remissions lasted from 6 months to 1 year in three patients and longer than 1 year in eight patients; five patients had remission periods that exceeded 2 years. These remission periods may be compared with patients’ follow-up status when last evaluated by the authors. On follow-up, 15 patients were asymptomatic for 1 year or longer (compared with eight remissions of similar duration). Twelve were asymptomatic for 2 years or longer (compared with five remissions of at least 2 years). The symptom-free follow-up period was 4 years for one patient, 6 years for three, and 8 years for two. It is noted that the majority of patients (16) were still having signs and symptoms of continuously or intermittently active pericarditis. In seven patients, the duration of the active process exceeded 5 years; in five patients, it exceeded 7 years; and in two patients, it actively persisted for 14 and 15 years, respectively.

What may be concluded from this natural history study that is germane to understanding the implications of the study by Guindo and coworkers? Prolonged symptom-free periods are not uncommon. In 15 of 31 patients, asymptomatic follow-up periods exceeded 1 year in the natural history study. This compares with an average of the longest remission periods in the Guindo et al study of less than 6 months. Hence, if the population studied by Guindo et al had been compared by some chance with the 15 patients alluded to above, the results would have been as good as with colchicine—a doubling of the average maximal remission duration by the drug, the benchmark used by the authors. The results reported in this issue of Circulation are quite dramatic; nevertheless, my illustration emphasizes the importance of controls, particularly when study populations are small. Therefore, there is a need for caution before we accept colchicine as the panacea for treatment of recurrent pericarditis. I share the editorial decision to report this study, which is somewhat flawed scientifically; the results are so dramatic that even in this small series of patients there is reason to anticipate efficacy, although the potential risk of drug toxicity with chronic administration is unknown and must be considered.

References


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