DOES COLCHICINE WORK? THE RESULTS OF THE FIRST CONTROLLED STUDY IN ACUTE GOUT

M. J. AHERN
Senior Lecturer, Department of Medicine, Flinders University of South Australia, SA

C. REID
Registrar in Rheumatology, Repatriation General Hospital, Daw Park, SA

T. P. GORDON
NH & MRC Research Fellow, Department of Clinical Immunology, Flinders Medical Centre, SA

M. McCREDIE
Senior Scientific Officer, Department of Rheumatology, Royal North Shore Hospital, NSW

P. M. BROOKS
Florance and Cope Professor of Rheumatology, University of Sydney, NSW

M. JONES
Biostatistician, Royal North Shore Hospital, NSW

Abstract:
We have performed the first controlled study of colchicine in acute gout, to determine its efficacy and toxicity, and to define the natural history of acute gout.

Two-thirds of colchicine-treated patients improved after 48 hours, but only one-third of the patients receiving placebo demonstrated similar improvement. The colchicine-treated patients responded earlier; significant differences from placebo were shown after 18-30 hours.

All patients given colchicine developed diarrhea after a median time of 24 hours (mean dose of colchicine 6.7 mg). This side effect occurred before relief of pain in most patients. (Aust NZ J Med 1987; 17: 301-304).

Key words: Colchicine, acute gout.

Colchicine has been used for centuries for the treatment of acute gout. In early Roman and Greek civilizations, extracts of various species of colchicum were used as purgatives, the rationale for their use in gout being based on Galen's humoral theory of disease. In 1763 Baron von Storck demonstrated that colchicum could be ingested in small quantities and suggested that patients with acute gout might benefit. In 1820, Pelletier and Caventou isolated an alkaloid from the corm of the autumn crocus *Colchicum autumnale* and thereby discovered colchicine.

Although acute gouty arthritis is usually self-limiting, it is widely believed that colchicine hastens recovery.[1] To our knowledge there have been no double blind trials to verify this dogma. Several open studies[2-6] imply efficacy of colchicine (whether given orally or intravenously) but these studies all have design faults which include absent or poor definition or criteria for response[2] and diagnosis,[3] few methodological details,[4] the use of analgesics,[3] and no measure of compliance. It is possible that these studies of colchicine in acute gout may simply be documenting the natural history of the condition. We therefore decided to carry out a controlled study of colchicine in proven acute gout.

PATIENTS AND METHODS

Forty-five in-patients (42 men, three women) with proven acute gout entered the study. Two patients were excluded because of their inability to understand visual analogue scales. All patients had the diagnosis of acute gout confirmed by joint aspiration and the demonstration of negatively

Reprint requests to: Dr M. J. Ahern, Department of Medicine, Flinders Medical Centre, Bedford Park, SA 5042.

TABLE 1
Comparison at Time 0 of Patients Taking Colchicine with Those Taking Placebo*

	Colchicine	Placebo
No. of patients	22	21
No. of joints involved	22	22
Large†	8	6
Small	14	16
Age (years) — mean ± SD	69 ± 8	70 ± 8
— range	55 – 85	56 – 91
Duration of symptoms (h)	38 ± 51	38 ± 29
Weight (kg)	71 ± 9	74 ± 11
Serum uric acid (mmol/l) (NR 0.12 – 0.45)	0.55 ± 0.16	0.50 ± 0.15
Serum creatinine (mmol/l) (NR 0.06 – 0.13)	0.14 ± 0.08	0.12 ± 0.03
Clinical score	9.5 ± 2.8	10.3 ± 2.4
Pain score	56 ± 21	68 ± 21

*No significant differences between the groups were detected using Student's *t* test.
†Large = knee, ankle, wrist; small = metatarsophalangeal, metacarpophalangeal, interphalangeal.

birefringent needle-shaped crystals using a polarizing light microscope with a first-order red compensator. Only minimal amounts of synovial fluid were extracted from the affected joints.

The remaining 43 patients (40 men, three women) were randomized (time 0) to one of two groups: to receive either oral colchicine ($n = 22$) or a matching placebo ($n = 21$). The initial dose of colchicine was 1 mg, followed by 0.5 mg every two hours until complete response or toxicity (nausea, vomiting, or diarrhea) occurred. No concomitant non-steroidal anti-inflammatory agents or analgesics were allowed 48 hours before entry or during the trial. This was verified by checking patients' medication charts where all administered medications, including analgesics, were recorded. In addition, resident medical and nursing staff were instructed not to treat symptoms of acute gout without first notifying members of the rheumatology service. Patients were assessed every six hours for 48 hours. Apart from drug therapy the two groups were managed identically. If toxicity occurred the medication was ceased and the assessments continued until 48 hours had elapsed from time 0.

Pain was measured using a visual analogue scale. A clinical score, which consisted of a compounded score comprising pain, tenderness on palpation, swelling, and redness graded on a four-point scale (none 0, mild 1, moderate 2, severe 3) was also used. The maximum score for any one joint was 12. The sensitivity of the parameters had been tested previously by assessing patients with acute gout treated with medium to high doses of indomethacin (250-300 mg/day). The visual analogue scale was more sensitive to change than the compounded clinical score. Each patient was assessed by the same person (M.A. or C.R.) throughout the trial. Ethics Committee approval had been obtained for the study and the informed consent of each patient had been given before entry into the study.

TABLE 2
Percentage of Joints in Colchicine and Placebo Groups which showed a 50% Decrease in Baseline Measures of Clinical and Pain Scores at Specified Intervals

	Hours after starting treatment			
	12	24	36	48
Clinical score				
Colchicine	5%	23%	50%**	64%*
Placebo	0%	0%	5%	23%
Pain score				
Colchicine	23%	41%	73%*	73%*
Placebo	9%	9%	32%	36%

*$p < 0.05$, **$p < 0.01$ by chi-square test.

Statistical Analysis

Student's *t* test, the chi-square test, and regression analysis were performed using SPSS on an IBM PCXT computer while the analysis of variance with repeated measures was carried out using BMDP on a VAX 11-750. Statistical significance was accepted at the 5% level.

RESULTS

Treated and placebo groups were similar with respect to age, duration of symptoms, and baseline clinical scores and visual analogue scales (Table 1). Using a 50% decrease in baseline measures as the criterion for improvement, a significantly greater proportion of those taking colchicine improved with respect to pain and clinical score, and did so earlier than the placebo group (Table 2). The more rapid improvement of the colchicine group can also be seen in Figures 1 and 2.

Regression analysis revealed that colchicine and the baseline scores (time 0) had a significant effect on outcome when measured by the clinical or the pain scores at 48 hours, explaining about 40% of the variance associated with these scores. Age,

TABLE 3
Analysis of Variance with Repeated Measures

	Outcome			
	Clinical score		Pain score	
Effect	*F*	*p*	*F*	*p*
Drug	3.03	0.09	3.71	0.06
Day/Night (D/N)	0.09	0.76	0.02	0.88
Drug × D/N	<0.01	0.95	0.03	0.87
Time	13.67	<0.0001	10.62	<0.0001
Time × D/N	0.99	0.44	1.71	0.10
Time × Drug	3.26	0.001	4.43	0.0001
Time × Drug × D/N	0.84	0.57	2.13	0.03

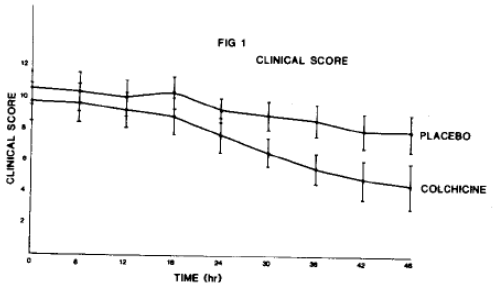

Figure 1: Change in the clinical score. Bars denote means ±95% confidence intervals.

weight, duration of symptoms, nature of joints involved, serum uric acid, and serum creatinine had no effect on the outcome.

Analysis of variance with repeated measures suggests an advantage of colchicine over placebo. Table 3 indicates that the differences in both pain and clinical scores between time points vary significantly between the colchicine and placebo groups. This is further supported by Table 4 which indicates that, although both groups improved over time, the colchicine-treated group improved at a significantly faster rate than the placebo group. The estimates in Table 4 were obtained by linear regression of pain and clinical scores on time.

There was no evidence of a diurnal effect on the assessment parameters (Table 3).

Toxicity

In all patients taking colchicine, diarrhea and/or vomiting occurred at a median time of 24 hours (range 12-36 hours) or after a mean dose of 6.7 mg of colchicine. The 50% improvement in the visual analogue score for pain occurred before toxicity in nine patients, after toxicity in 12 patients, and concurrently in one. The 50% improvement in the clinical score occurred before toxicity in two, and afterwards in 20 patients.

Five patients developed nausea while taking placebo.

DISCUSSION

Traditionally colchicine has played a major role in the management of acute gout and for many physicians it is the drug of choice because of the alleged rapidity of its effect.[7] This belief originated from quasi-experimental open studies, which did not document the rapidity of its effect.

Our controlled double blind study of colchicine in acute gout has demonstrated that both placebo- and colchicine-treated inpatients improved with time but that the colchicine-treated patients responded earlier. Using Wallace's criteria[3] for major improvement (a greater than 50% improvement in objective manifestations: erythema, swelling, tenderness), two-thirds of the colchicine-treated patients responded within 48 hours. This compares favourably with Wallace's response of 76% in his open study of colchicine. Using the same criteria, about one-third of patients treated with placebo improved within 48 hours. This is consistent with the self-limiting nature of acute gout.

Two aspects of the study design need further amplification. In-patients were chosen to fulfil entry criteria, to ensure drug compliance, and to make possible frequent assessments within the first 48 hours. Secondly, the patients were entered into the study after the rheumatology service was notified and the diagnosis of acute gout confirmed. This meant a delay of a mean of 38 hours from onset of symptoms. This delay occurred despite wide publicity within the hospital, several educational programmes directed at the resident and nursing staff before the commencement of the study, and a 24-hour rheumatology service. Seventy per cent of the patients had suffered previous episodes of acute gout and only a minority of these patients were aware that treatment should be begun early. This suggests that most patients with acute gout initiate treatment only after the attack has become established. Ideally colchicine should be used as early as possible, but in practice this does not appear to occur. We believe the delay in initiating treatment of established acute gout in our in-patient population reflects clinical hospital practice.

The pain scores showed significant difference between colchicine and placebo after 18 hours, whereas the clinical scores did not become significantly different until after 30 hours. This discrepancy is explained by the pain response occurring earlier than the other clinical score components such as edema and erythema (data not shown).

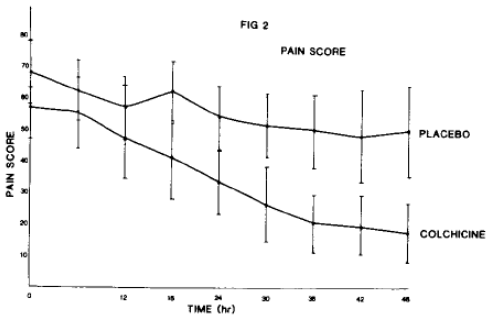

Figure 2: Change in the pain score. Bars denote means ±95% confidence intervals.

TABLE 4
Estimates of the Trend in Clinical and Pain Scores over Time for Both Groups

	Outcome					
	Clinical score			Pain score		
Group	Trend	SE	t	Trend	SE	t
Colchicine	−0.12	0.01	−11.20*	−0.91	0.11	−8.27*
Placebo	−0.06	0.01	−5.29*	−0.46	0.11	−2.88*
Difference (colchicine − placebo; rounded)	0.07	0.02	4.18*	0.45	0.15	2.92*

*$p < 0.05$

Can the late effect of colchicine in acute gout be explained by our current knowledge of its effects at the cellular level? Colchicine has been shown to:

(1) suppress the generation and release of a urate-crystal-induced chemotactic factor from neutrophils,[8]
(2) reduce the phagocytic capacity and phagocytic rate of neutrophils,[9] and
(3) increase cellular levels of cyclic AMP with inhibition of lysosomal enzyme release.[10]

Of the three cellular effects the first is most consistent with the data, indicating that although colchicine is generally a weak anti-inflammatory agent it has a major anti-inflammatory effect in acute gout. This cellular effect is also consistent with the therapeutic response occurring after 18-30 hours, by impairment of recruitment of neutrophils to the sites of inflammation.

There appear to be no studies comparing the rapidity of effect of non-steroidal anti-inflammatory drugs with colchicine. Several studies have shown good response within 24 hours using fenoprofen,[11] naproxen,[12] or isoxicam,[13] but these were either open studies or did not define criteria for response. Since improvement in acute gout is inevitable, the important outcome is the rate of improvement, and this has not been defined for any of the non-steroidal anti-inflammatory drugs.

In contrast with current opinion,[1,7,14] we did not find that the duration of symptoms before initiating treatment had any effect on the outcome at 48 hours. Because all our patients had established acute gout before entry, the design of the study may have prevented this factor being important.

All our patients given colchicine developed evidence of toxicity with diarrhea and/or vomiting. Toxicity occurred before there had been a major improvement in the clinical score in 91% of patients on colchicine. In retrospect, if we had ceased therapy once there had been an improvement of 50% of the baseline pain score, then toxicity would have been reduced by 41%. Nevertheless, toxicity would still be expected in the majority. Because of its inevitable occurrence, the blindness of the study after toxicity was threatened, but this did not appear to be an important factor as the slopes of the lines in Figures 1 and 2 do not alter at 24 hours.

This study has defined the natural history of established acute gout in hospital patients and demonstrated that colchicine significantly hastens recovery, although toxicity occurred before major improvement in most of the colchicine-treated patients. We would recommend that oral colchicine be used only in those patients in whom effective and less toxic non-steroidal anti-inflammatory agents are contraindicated.

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