# Colchicine Analogs in the Treatment of Acute Gout

*By* STANLEY L. WALLACE

**Five colchicine analogs were tested for their effects on the clinical manifestations of acute gouty arthritis. The preparations demonstrating some degree of benefit were desacetylmethylcolchicine, desacetylthiocolchicine, trimethylcolchicinic acid and colchicoside. The remaining preparation, colchiceine, was ineffective.**

**Cinque analogos de colchicina esseva testate pro lor effectos super le manifestationes clinic de gutta acute. Le preparatos que demonstrava un certe grado de beneficio esseva disacetylmethylcolchicina, disacetylthiocolchicina, acido trimethylcolchicinic, e colchicosido. Le quinte preparato, colchiceina, esseva inefficace.**

COLCHICINE and extracts of the plant *Colchicum autumnale* have been used empirically in the treatment of acute gout for 1500 years,[1] and as yet little is known as to the mechanism of colchicine's beneficial effect. The most important known action of this substance is its ability to arrest mitosis. This was first described by Lits[2] and Dustin[3] in 1934, and in 1935 Amoroso[4] first noted the beneficial effects of colchicine in the treatment of human tumors.

The chemical structure of colchicine (fig.1) was finally established in 1945.[5] Many modifications of the colchicine molecule have been produced and tested as antimitotic agents.[6-11] Extensive investigations of the relationship of colchicine's chemical structure to its biologic antimitotic activity have been made in these same studies. No similar evaluations have been made of colchicine and its analogs as anti-gout agents. Desacetylmethylcolchicine[12-14] and colchicoside[15,16] have been used, however, in the clinical treatment of acute gout.

It is the purpose of this paper to report the results of the use of five selected colchicine analogs in the treatment of acute gout. An evaluation has been made of the relationship between the anti-gout and antimitotic effects of these analogs, and of the possible chemical configuration necessary for colchicine's activity against gout.

## MATERIALS AND METHODS

The colchicine analogs used were desacetylmethylcolchicine (DMC), colchicoside, desacetylthiocolchicine (DTC), trimethylcolchicinic acid (TMCA) and colchiceine (figs. 2a–e). The relation that each compound has to the parent colchicine can be determined readily from figure 2. In colchicoside, a glycoside has been substituted for the first methyl group on the first ring of the colchicine molecule. A methyl group replaces the acetyl

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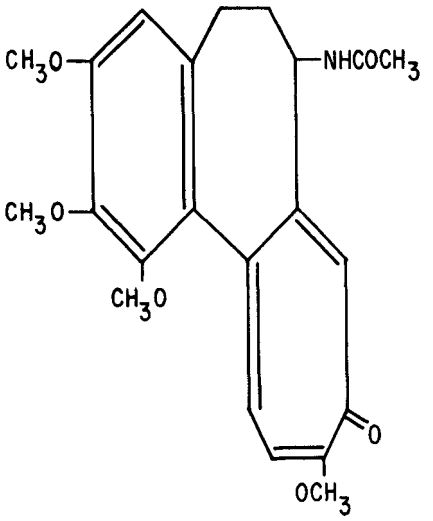


**Fig. 1.—Colchicine.**

group on the side chain of the second ring in DMC. In DTC, there are two areas of substitution: in the side chain of the second ring the acetyl group is absent, and sulfur replaces the oxygen in the methoxy radical attached to the third ring. In TMCA, the substitutions are in the same places as in DTC. The acetyl radical has again been removed from the side chain on the second ring, and a hydroxy group replaces the methoxy group on the third ring. Colchiceine most likely exists in the form of a derivative of isocolchicine rather than colchicine,[17] with an hydroxy group replacing the methoxy group on the third ring of isocolchicine.

DMC, TMCA and colchiceine were given orally. Colchicoside and DTC were available only as intravenous preparations. Doses were selected as the approximate equimolecular equivalents of therapeutic amounts of colchicine (table 1). All analogs were given in single total doses rather than fractionally.

All patients reported here as treated with these colchicine analogs had acute gout. They demonstrated acute arthritis, associated in all with hyperuricemia. In most patients, there had been preceding acute attacks of gout, and many had had typical responses to the administration of colchicine. In these patients the diagnosis of recurrent acute gout was well established. No patient was included in this series in whom the diagnosis of acute gout was uncertain.

A good response to therapy with any of the analogs was arbitrarily defined as the 75 per cent or greater clearance of all objective manifestations of acute gout within 48 hours after therapy. All but three of the estimations as to percentage clearing were made by one observer (S. L. W.). This arbitrary criterion for successful therapy has not been completely satisfactory; in some patients, partial responses to therapy, less than 75 per cent clearing, occurred. For the purposes of this study, however, some definition of specific response to therapy was necessary. Most of the patients showing inadequate response to the colchicine analogs were then given oral or intravenous colchicine in therapeutic doses. This was done to determine the susceptibility of these individual episodes of acute gout to any colchicine-like agent.

## Results

Results are summarized in table 1. DMC, DTC and TMCA were effective anti-gout agents. Six of eight patients responded to DMC with at least 75 per cent clearance. Four of five each responded to DTC and TMCA. Col-

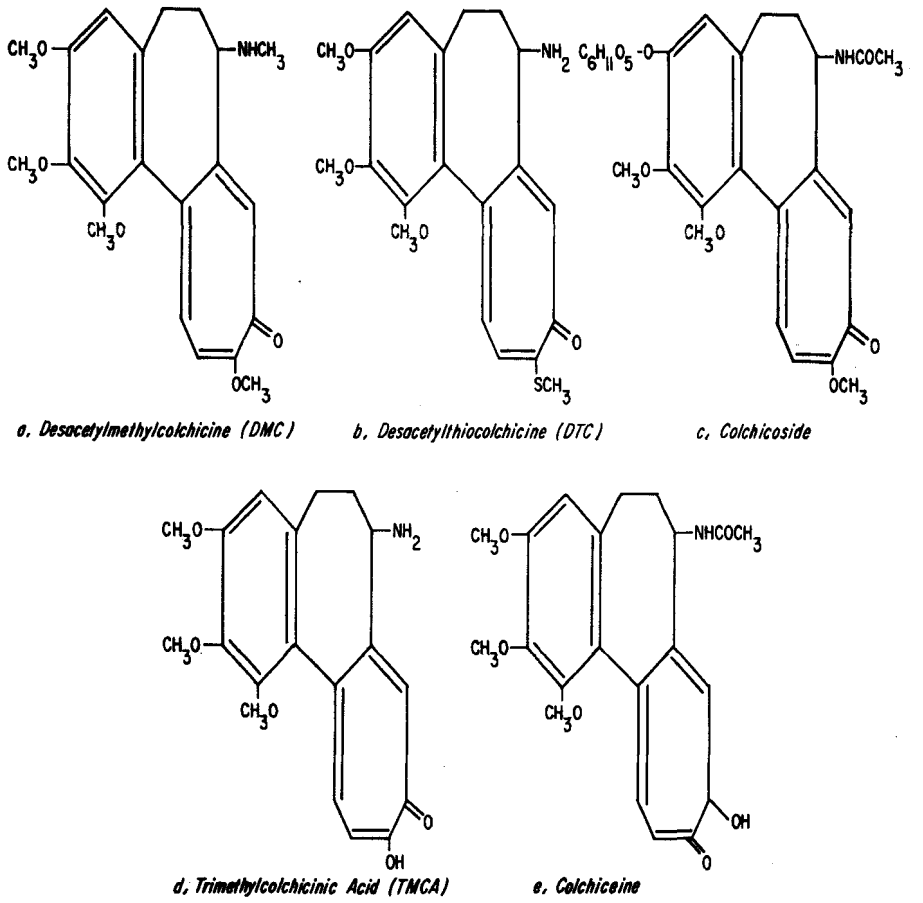


**Fig. 2.—Colchicine analogs.**

chicoside, given intravenously in a single dose of 15 mg. in nine of 10 patients, had some effect against gout, but definitely less than the parent colchicine. Oral colchiceine not only did not produce 75 per cent or more objective improvement in any of the five patients to whom it was given but had no measurable influence on the disease process at all. Four of the five patients failing to respond to this agent then went on to improve satisfactorily with colchicine.

There was no serious toxicity in the patients with gout treated with any of these agents. One patient each treated with DMC, DTC and colchiceine developed mild diarrhea. None of the patients showed the degree of gastrointestinal disturbance seen so frequently with colchicine.

One patient with subsequently proved rheumatoid arthritis not included in this series was given 5 mg. of DMC orally as a diagnostic and therapeutic test. He developed a moderate granulocytopenia which finally cleared after four months. No other hematologic toxicity was seen and no skin or hair changes were observed in a subsequent follow-up of a year or more.

Table 1.—*Colchicine Derivatives in the Treatment of Acute Gout*

| | Dose and Route | Patients with Acute Gout | Good Responses | Poor Responses | Responses of "Failures" to Colchicine |
|---|---|---|---|---|---|
| Desacetylmethyl-colchicine | 5–7 mg. orally | 8 | 6 | 2 | 0 |
| Colchicoside | 15–30 mg. I.V. | 10 | 4 | 6 | 2 of 4 |
| Desacetylthio-colchicine | 5 mg. I.V. | 5 | 4 | 1 | 1 |
| Trimethyl-colchicinic acid | 5–6 mg. orally | 5 | 4 | 1 | 0 |
| Colchiceine | 5–8 mg. orally | 5 | 0 | 5 | 4 |

## Discussion

It is clear that modifications of the basic colchicine structure can be made which will retain the anti-gout effect while almost completely eliminating the gastrointestinal disturbances produced by colchicine. The work reported here can be considered as a preliminary screening of colchicine analogs in acute gout, in the search for an effective anti-gout agent without toxicity.

DMC cannot be considered a satisfactory alternative to colchicine. Although it is as effective as colchicine[14] and has little or no gastrointestinal toxicity, in humans it has been shown to have a markedly greater potential for anti-mitotic activity in the bone marrow and skin than the parent colchicine. Many reports[14,18-22] have been made of agranulocytosis and/or depilation following the use of this agent in acute gout. As little as 5 mg. has produced a moderate granulocytopenia and 10 mg. of DMC[22] produced a profound agranulocytosis in one patient. DMC has been used with some success in the treatment of chronic myelogenous leukemia.[23,24] Further use of this drug in the treatment of acute gout is potentially dangerous.

DTC also was effective in the treatment of acute gout; in the five patients reported here there was no toxicity. However, DTC, like DMC, has been reported as effective in the treatment of chronic granulocytic leukemia.[25,26] In the rat, prolonged administration produced agranulocytosis.[27] It seems likely that, with the further use of DTC in the treatment of acute gout, agranulocytosis would ultimately be seen.

Colchicoside, given as a single intravenous dose, although it had some anti-gout effect, was not a satisfactory substitute for colchicine in the patients reported here. Mugler and Grappe[15] used this analog of colchicine in the treatment of 20 patients with acute gout with excellent results and with no significant side effects. In general, however, they gave larger total doses over a longer period of time. Krewer[16] reported 19 excellent and 6 moderate results in 33 gouty patients and 5 with other disorders treated with colchicoside. The drug produced no toxicity. Prolonged administration of colchicoside in the rat failed to cause any significant white cell depression.[27]

TMCA was an effective drug against acute gout in four of the five patients in whom it was tested. No toxicity was seen in this small group. In experi-

mental studies, this compound has been shown to have no antimitotic effect against mouse sarcoma,[6] chick fibroblast tissue cultures,[28] regenerating rat liver cells[29] and rat corneal epithelium.[7] Further clinical studies with this agent are in progress.

There is a notable disparity between the potent effect of TMCA against gout and its lack of antimitotic activity, at least in the experimental tissues studied. This disparity argues for the lack of relation between these two actions of colchicine. Further evidence for the non-parallelism between the anti-gout and antimitotic effects of colchicine and its analogs can be adduced from the experience with DMC. With this compound, anti-gout activity of the same order as colchicine is combined with a significantly augmented antimitotic potentiality in the human.

Colchiceine given orally had no value in the treatment of acute gout. This might be explained on the basis of intrinsic ineffectiveness or of failure of absorption. There is indirect evidence for colchiceine's absorbability. It is soluble as a sodium salt or in dilute alkaline solution.[9] Its solubility is not markedly different from that of TMCA,[30] which certainly is absorbed. Finally, one patient given colchiceine therapeutically developed mild diarrhea. Ferguson[31] has shown that colchicine diarrhea is primarily a central rather than a local gastrointestinal phenomenon.

If colchiceine is absorbed, then its lack of anti-gout activity may be due to the isomeric modification in the third ring.[17] Leiter et al.[11] have shown that isomerization here removes antimitotic activity as well, although experience with TMCA shows that these two colchicine effects need not be related. Simple substitution on the third ring without isomerization (as in DTC and TMCA) does not remove effectiveness against acute gout.

## Conclusions

1. Five colchicine analogs have been tested in the treatment of acute gout. Desacetylmethylcolchicine (DMC), desacetylthiocolchicine (DTC) and trimethylcolchicinic acid (TMCA) were effective, colchicoside mildly effective, and colchiceine ineffective as anti-gout agents.

2. Both DMC and DTC may produce agranulocytosis, whereas TMCA has not been shown as yet to cause similar toxicity.

3. Experience with TMCA implies that the anti-gout and antimitotic effects of colchicine and its analogs can be separated.

4. The postulate has been made that the specific configuration of the side chains on the third ring of the colchicine molecule is necessary for its anti-gout effect.

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