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Adverse Effects Encountered with Colchicine: A Three Centre Study

KEYWORDS: Colchicine, gout, gouty arthritis, adverse effects, gastrointestinal side effects, low-dose colchicine

Dr V Marwaha
MD DNB, Senior Advisor (Medicine & Rheumat), Chandimandir

Dr A Singhal
MD DNB, PDCC Rheumatologist, Asvini Hospital, Mumbai

Dr GD Choudhary
MD, Rheumatologist, Command hospital, Kolkata

DR V Hande
MD, HoD (Medicine), Asvini Hospital, Mumbai

ABSTRACT ***Objective:*** *Colchicine is a useful drug to treat acute attacks of gout or to prevent attacks of gout. Side effects with this drug include diarrhea, nausea, cramping abdominal pain and vomiting. Other adverse effects include bone marrow depression, peripheral neuritis, purpura, or myopathy.*

Methods: *This was an observational and prospective study conducted in three centers at Northern, Western and Eastern parts of India from January 2014 to August 2014. Patients with history of intolerance to colchicine were excluded from study. Patients were given a dose of 0.5 mg colchicine tablet twice daily. The adverse effects of the drugs were recorded and patients were advised to stop the drug on occurrence of any adverse event. The duration of treatment ranged from 5 days to 3 months.*

Results: *A total of 186 patients (Men=166 and women=20) were enrolled. Average age at the time of diagnosis was 48 years. Seven patients (3.76%) discontinued the drug. Out of them 5 had developed diarrhea, 01 had developed colicky abdominal pain with diarrhea, and 01 had nausea with diarrhea. All patients developed gastrointestinal symptoms within 72 h of taking the drug.*

Conclusion: *Low-dose colchicine (0.5 mg twice daily) causes less adverse effects and is usually well-tolerated. However, patients have to be cautioned about the gastrointestinal side effects for optimum compliance.*

Introduction

Colchicine is a major alkaloid derived majorly from Colchicum autumnale. Colchicine exhibits anti-gout and anti-inflammatory activities. The 2012 American College of Rheumatology guidelines on management of gout viewed low-dose colchicine as equivalent to non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids for treating acute gout.[1] Colchicine is combined with NSAIDs or corticosteroids when treatment is desired for severe acute gout. In addition, colchicine is used as a prophylactic for recurrent gouty arthritis. The anti-inflammatory effect of colchicine is attributed to its ability to disrupt microtubules in neutrophils by interrupting the dynamics of microtubules, which disrupts mitosis and thereby inhibits the migration of neutrophils and other inflammatory cells toward the chemotactic factors.[2,3] Prophylactic treatments is needed for some months, even after achieving normal serum urate levels.

Colchicine is viewed as a beneficial treatment option in acute gout, but is associated with high rates of gastrointestinal adverse events. In a study by Ahern et al., patients developed diarrhea after a median time of 24 h (mean dose of colchicine [6.7] mg) and the side effect was evident even before the patients were relieved of pain.[4] Despite the use of colchicine as one of the first-line therapeutic options for the treatment of acute gout, data on the safety and tolerability of colchicine is limited. We conducted a study to observe the adverse events associated with low-dose colchicine.

Materials and methods

We conducted an observational and prospective study in three centers at Northern, Western and Eastern parts of India. We enrolled patients from January 2014 to August 2014. Patients with history of intolerance to colchicine were excluded from study. Patients were treated with 0.5 mg colchicine tablet, twice daily. The duration of treatment ranged from 5 days to 3 months. Patients were well-informed about the adverse effects of the drug and were asked to report any adverse events to the principal investigator. Patients were asked to stop the drug on occurrence of any adverse event.

Results

One hundred and eighty-six patients were enrolled into the study. The study population comprised predominantly men (N=166) and only 20 women were in the study. The average age of the study population was 48 years. Seven patients discontinued the drug and out of them 5 developed diarrhea, 1 developed colicky abdominal pain with diarrhea, and 01 developed nausea with diarrhea. All these patients developed gastrointestinal symptoms within 72 h of start of the drug.

Discussion

Colchicine is used in the treatment or prophylaxis of gout as it reduces the inflammatory responses to deposited urate crystals. The clinical burden of gouty arthritis is well-established, nevertheless, its diagnosis and management remains a challenge because it is often misdiagnosed and mismanaged. Acute gout is usually treated with NSAIDs, colchicine, corticosteroids, or a combination of two agents. To reduce the serum urate levels, the treatment is combined with uricosuric agents or uric acid reabsorption inhibitors.[5]

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Colchicine is the most common drug that is prescribed from the time of diagnosis in emergency or in-clinic through discharge up to follow-up. In a real world retrospective study, 60.8% of patients in the colchicine group were prescribed colchicine consistently from time of diagnosis in emergency through discharge up to follow-up. In the same set-up, 26.8% and 17.7% of patients in the respective cohort were prescribed consistently NSAIDs and systemic corticosteroids.6 The common side-effects of colchicine include diarrhea, nausea, cramping abdominal pain and vomiting. Other adverse effects include bone marrow depression, peripheral neuritis, purpura, or myopathy. Although, colchicine is used as one of the first-line therapeutic options for the treatment of acute gout, data on the safety and tolerability of colchicine is limited.

In our study, low-dose colchicine was associated with fewer side-effects, especially gastrointestinal side-effect. A review of literature also reveals that low-dose colchicine has a far better safety and tolerability, with exception of high incidence of gastrointestinal side-effects, compared to high dose colchicine.[7–10]

Khanna et al. conducted a systematic review of randomized control trials on pharmacologic and non-pharmacologic agents used for the treatment of acute gouty arthritis.[10] In their review, they found that the tolerability profile of low-dose colchicine was comparable to placebo and significantly lower than high-dose colchicine.[7] A systemic literature review on anti-gout therapies reported that the safety profile of low-dose colchicine did not differ from that of placebo but it was safer than high-dose colchicine.[8] According to a Cochrane review published in 2006, colchicine was found to have low benefit to toxicity ratio. The number needed to treat (NNT) with colchicine versus placebo, with respect to alleviation of pain and clinical symptoms (such as tenderness on palpation, swelling, redness, and pain) was 3 and 2, respectively. Gastrointestinal side-effects (diarrhea and/or vomiting) was reported by all subjects in colchicine arm and the number needed to harm (NNH) with colchicine versus placebo was 1.9 An update to the Cochrane review first published in 2006 concluded that the evidence for efficacy of low- and high-dose colchicine in treating acute gout is of low-quality. The NNT to benefit was 4 and 5 for high- and low-dose, respectively. Adverse events such as diarrhea, vomiting or nausea caused by high-dose colchicine were much greater than placebo with NNH of [2]. However, there are no additional adverse events of diarrhea, nausea or vomiting with low-dose colchicine compared to placebo.[10]

Case reports on chronic renal failure/renal transplant and gout showed that colchicine was associated with colchicine-induced myoneuropathy, which was reversible after its discontinuation.[11,12] Cardiac transplant patients with concomitant renal insufficiency who were treated with colchicine for cyclosporin A-induced gout developed colchicine-induced myoneuropathy. In these patients, colchicine-induced myoneuropathy was regressed by lowering the dose or discontinuing colchicine.[13] In acute gouty arthritis with comorbid renal impairment, colchicine should be used at a dose of 500 µg three times a day or less frequently.[14] In our study, we did not enroll patients with comorbid conditions. Serious toxic reactions to colchicine could be avoided if it is used in accordance to the guidelines.

Conclusion

Colchicine is an effective treatment option for alleviating pain and clinical symptoms of acute gout. However, there are concerns about the safety and tolerability of colchicine, especially with the use of high dose. In our study, we found that low-dose colchicine (0.5 mg twice daily) causes less adverse effects and is usually well-tolerated. However, patients have to be cautioned about the gastrointestinal side effects for optimum compliance. A reduction in frequency of dosing may reduce the adverse effects of colchicine in patients with or without comorbid conditions.

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