ColciGel®: A Superior Alternative for Acute Gout Flares

By Gary E. Myerson, MD | Arthritis & Rheumatology of Georgia, P.C.
Marc Alan Brenner, DPM, The Institute for Diabetic Foot Research
Robert L. Wilbur, Pharm.D., CPh | Director, Medical Affairs, Gensco Pharma

ColciGel®

A new agent, ColciGel®, has recently emerged for the treatment of acute flares of gout. ColciGel is a transdermal gel preparation of Colchicinum (colchicine in its homeopathic state) that is applied topically. ColciGel contains Colchicinum 4X in a proprietary Organogel that is applied directly to the site of acute flares. It is supplied as an airless 15ml container that delivers 0.25 ml of ColciGel® per pump. When ColciGel® is applied to the site of the acute gout flare, it crosses the dermal layer and reduces the inflammation and pain associated with the flare. With the topical application of ColciGel®, only minimal amounts of colchicine enter systemic circulation, reaching sub-clinical concentrations of <50 pg/mL. The combination of avoiding the gastrointestinal (GI) system and sub-clinical systemic circulation allows ColciGel® to avoid the tolerability and safety issues commonly seen with **oral** colchicine. ColciGel® patients report a 50% or greater decrease in pain and inflammation within a few hours and improved pain relief with additional applications. The typical GI side effects usually seen with **oral** colchicine have not been observed with transdermal ColciGel®.

Problems with Current Therapies

The primary goal in the treatment of an acute gout flare is the reduction in pain and inflammation. The current American College of Rheumatology (ACR) treatment guidelines for acute gout flares[1] are clear in stating that the sooner treatment to reduce the pain and inflammation is initiated (within 24 hours of onset) the greater the response. Conversely, the longer the delay in treatment, due to waiting for physician appointment or attempting treatment with an ineffective agent (NSAIDs or oral colchicine), the less likely the patient will experience a positive outcome and often lead to further healthcare costs.

The ACR guidelines for acute gout flares include use of non-steroidal anti-inflammatory drugs (NSAIDs), oral colchicine, and corticosteroids to achieve this goal.[1] However, there are significant concerns with each of these therapeutic options.

Most patients experiencing an acute gout flare will initially self-medicate with an OTC NSAID, either alone or in combination with another drug (ie, oral colchicine) and may not achieve significant pain relief. Many of these patients, most of whom are over the age of 60, will have co-morbidities such as cardiovascular disease which may preclude the prolonged use of high doses of NSAIDs due to the increased risk of heart attacks and strokes, as outlined in the Black Box warning for this drug class.[2]

Oral colchicine, though used for centuries to treat gout flares, is only modestly effective yet associated with a high degree of toxicity and adverse drug events. A clinical study in 2009 of high- and low-dose oral colchicine in treating gout flares demonstrated that the low-dose treatment was more effective and better tolerated by patients.[3] With FDA approval of Colycrs in 2012, the low-dose became the only approved and indicated dose for treating acute flares of gout.[4]

The clinical evidence supporting low-dose oral colchicine was reviewed by van Echteld and stated that: "Based upon only two published trials, there is low-quality evidence that low-dose (oral) colchicine is likely to be an effective treatment for acute gout.".[5] The clinical trial of low-dose oral colchicine versus high-dose oral colchicine had 184 patients in 3 groups (placebo was the 3rd group) treated for 1 day. In the low-dose group, pain relief was achieved in only 38% of patients but was better than in the high-dose group (33%) and placebo (15%). Oral colchicine therapy was not effective in most of the cases with 62% of low-dose patients and 67% of high-dose patients not achieving significant pain relief.[4]

Oral colchicine can be associated with a very high rate of adverse events. About 80% of high-dose patients have GI side effects.[3] These typically are diarrhea, nausea, vomiting, and abdominal cramps. Morris et al. in discussing oral colchicine therapy stated: "The side effects of nausea, vomiting, or diarrhea are particularly difficult to endure in patients who are in pain, incapacitated, and immobile from acute gouty arthritis.".[6] Side effects are fewer with the low-dose,[3,7] although low-dose oral colchicine also can be associated with diarrhea, abdominal cramps, nausea, and vomiting.[7] Borstad reported that 38% of patients treated with low-dose oral colchicine had diarrhea as a side effect compared with 4.5% of patients in the placebo group.[7] The GI side effects from oral colchicine can be serious. The diarrhea can be severe and lead to dehydration and hospitalization.[8] The majority of hospitalizations of patients with gout are associated with the use of oral colchicine.[8]

One of the reasons that oral colchicine can have serious adverse effects is that there is a strong potential for Drug-Drug Interactions (DDIs) with oral colchicine therapy. Colchicine is metabolized by the cytochrome P450-3A4 (CYP3A4) and transported by P-glycoprotein (Pgp).[9] Co-administration with

inhibitors of CYP3A4 or Pgp can lead to increases in colchicine concentrations in circulation.[9] Since the concentrations at which colchicine is effective are just slightly below that which cause toxicity, circulating concentrations of colchicine can be raised to toxic levels by DDIs. The list in the Colcrys PI of drugs that can cause DDIs includes 26 drugs plus grapefruit juice.[2,8] Oral colchicine can also cause rhabdomyolysis (myopathy) which can be exacerbated by concomitant use of cholesterol-lowering drugs that are associated with myopathy (statins and fibrates).[2] This concern adds 8 more drugs (many of them commonly used) to the list of drugs with a potential for significant DDIs with oral colchicine.[2] Colchicine toxicity is very serious and can have fatal consequences.[2] One hundred and seventeen deaths have been reported for colchicine with oral, IV or intramuscular administration. Over half of these deaths have been attributed to DDIs.[9]

Corticosteroids are considered the last of the first line treatment agents due to the high oral doses needed and the likelihood of rebound attacks when the steroid is quickly tapered down.[10] These drugs are most effectively administered as an intra-articular injection in a physician's office or emergency room setting, quelling the inflammation but generating more treatment cost.

Conclusion

ColciGel® is a first line agent in the treatment of acute gout flares and an alternative to oral colchicine in those patients who experience either adverse drug effects (ADRs) or who do not achieve suitable symptom relief. Considering that up to 80% of patients taking oral colchicine experience some level of associated ADRs, such as Nausea, Vomiting, Diarrhea, and or Abdominal Cramping,[3,4] and only 38% of these patients achieve a 50% or greater relief in pain,[4] patients and clinicians need a better alternative. ColciGel®, administered topically at the site of inflammation thereby bypassing the gastrointestinal tract (and associated ADRs), is that superior alternative.

Summary of ColciGel® Research

ColciGel®, developed by Gensco Pharma, is a 4X attenuation of Colchicinium, the homeopathic designation of colchicine, combined with a patented enhanced transdermal base. The hypothesis was that a low concentration of Colchicinium could be applied to the site of a gout flare, interrupting the inflammatory cascade and eliciting a positive clinical outcome without the adverse effects associated with oral colchicine formulations. This hypothesis was supported by earlier research demonstrating the favorable transdermal properties of colchicine[11] and the effective mitigation of inflammation, secondary to monosodium urate (MSU) crystals, in animal models via a transdermal route of administration.[12] The hypothesis has been validated by the following testing and clinical trials.

Samples of the transdermal Colchicinium gel formulation were tested In-Vitro for drug release and diffusion across a synthetic skin model (Franz cell diffusion). The results demonstrated a high drug release rate and significant transmembrane diffusion (flux).

Once the favorable in vitro characteristics of ColciGel® were established, animal testing to model the pharmacokinetic and safety profile of this drug began. Testing in rabbits, utilizing single and multiple high dose applications, produced only minimal serum presence and no signs of toxicity or dermal irritation. Extrapolation of this data to a human model indicated an expected serum level below clinical significance.

Human PK testing was conducted in healthy volunteers utilizing single dose and multiple dose (dose stacking) applications of ColciGel®. Serial serum sampling resulted in no detectable presence of colchicine in any of the subjects. Again, there were no signs of toxicity or adverse drug reactions (ADR) including dermal irritation. These results support the belief that ColciGel® will not exhibit the same degree of drug – drug interactions (via the P450 3A4 hepatic enzyme pathway) and associated toxicities seen with oral colchicine. Furthermore, these results and the novel route of administration provides confidence in the assertion of minimal gastrointestinal (GI) adverse events, as are common in the oral formulation.

A proof of concept test in a small cohort of patients[13] with acute GF was conducted by physicians experienced in gout treatment. The results were impressive with all patient experiencing a 50% or greater reduction in pain within 48 hours of initial application and improved pain relief with additional applications. Many of these patients reporting a significant decrease in pain and inflammation within a few hours of initial application. None reported any ADRs including dermal irritation or GI distress. This preliminary data strongly supports the efficacy of ColciGel® in the treatment of acute gout flares.

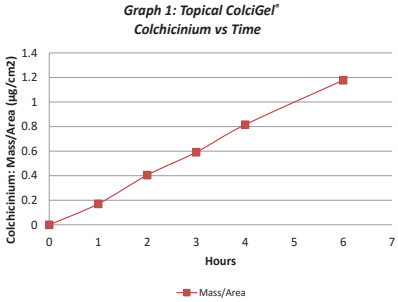
The next step for Gensco is a post marketing surveillance study looking at greater numbers of patients and sub groups for efficacy variations and incidence of reported ADRs. This post marketing open label study is currently preparing for launch.

Summary of Critical Tests

Diffusion

To assess transdermal permeation of ColciGel®, an in-vitro test was conducted utilizing a vertical diffusion cell process. In this test 384 mg of ColciGel® was applied to 0.6446 cm^2 surface area of a polyethersulfone membrane with a thickness of 0.45 micrometers. The permeation process was evaluated over six hours by sampling the reactor fluid hourly. The amount of colchicinium in the samples was determined by High Performance Liquid Chromatography. The results are shown in Graph 1.

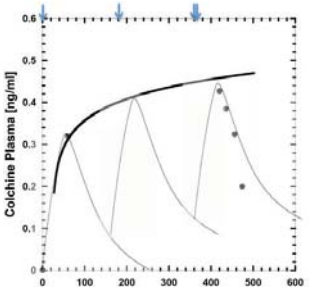
The results demonstrate significant transmembrane drug diffusion supporting the transdermal route of administration for ColciGel®.



Systemic absorption in Animal Model

In a Gensco sponsored study, six New Zealand White Rabbits were administered a single 375 microliter dose of ColciGel® containing, 7.5 micrograms of colchicinium, to a shaved dorsal area measuring 2.5 cm by 2.5 cm. Serum analysis demonstrated 90% of the applied dose was absorbed yielding a peak serum concentration of 0.26 nanogram / milliliter +/- 0.09 nG/mL (Tmax of 60 minutes).

Graph 2: Single Dose ColciGel® Pharmacokinetics



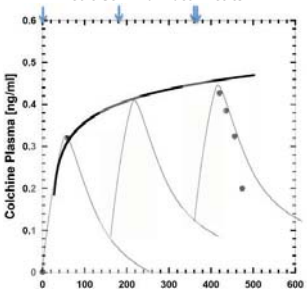
The kinetics of colchicine plasma levels:
T1/2a = 30 min
Absorption rate constant (ka) = .693/.5h = 1.4/h
T1/2e = 65 min
Elimination rate constant (ke) = .693/1.1h = .64/h
Total plasma absorbance = 90% (AUC)
Cmax = 0.26 ng/ml ± 0.09 ng/ml
Tmax = 60 min

In this same study four additional rabbits were administered a dose of 375mcL of ColciGel® every three hours for a total of three doses in the same manner as in the single dose experiment. Serum analysis showed a peak serum level, one hour after the third dose application, of 0.45 nG/mL. A steady state serum level of 0.5 nG/mL was calculated to occur after the fifth hourly dose.

None of the animals demonstrated any signs of dermal irritation or injury at any time during or after this study.

The dosing used for these rabbits, based on volume of distribution and animal weight, represents a human dose 16 times greater than the standard recommended therapeutic dose. An extrapolation of this data indicates a human PK model serum level of 8 - 16 picograms / ml based on a typical therapeutic dose.

Graph 3: Multiple Dose ColciGel® Pharmacokinetics



Arrows indicate dosing events.
Double arrow indicates final dose.
Single-dosing kinetic curves overlay the data.
Bold line is logarithmic progression prediction built to data.

Pharmacokinetic Modeling in Humans

In a pharmacokinetic study evaluating systemic absorption of ColciGel® in humans, six healthy volunteers where randomized into 2 groups. The first group of three subjects received a single 0.75 mg dose of ColciGel® applied topically to the base of the great toe on the right foot. Serum samples were collected from each subject every 30 minutes, post dose, for a total of 8 samples.

The second group of three subjects received a dose of 0.75 mg of ColciGel® every 60 minutes for a total of four doses. The ColciGel® was applied to the base of the great toe on the right foot, as in the single dose group. Serum samples were collected at 0, 120, 180, 210, 240, 270, 300, and 360 minutes after the first dose application, for a total of eight serum samples.

All serum samples were analyzed by tandem HPLC/MS separation and quantification to measure colchicine down to a concentration of 0.05 ng/ml (50 pg/ml). None of the 48 serum samples analyzed measured above the 0.05 ng/ml level. This confirmed the animal testing data that predicted a human serum level of less than 50 pg/ml (estimated 8 – 16 pg/ml).

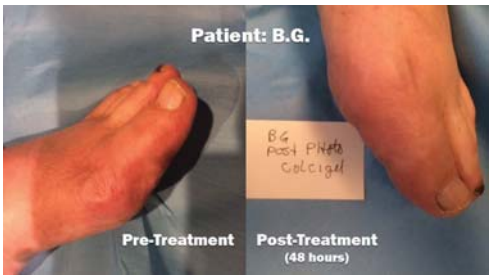
A single oral 0.6 mg dose of colchicine has been shown to elicit a mean serum level of 2.5 ng/ml in healthy volunteers. ColciGel®, due to its overall low colchicinium dose, is absorbed systemically in minute quantities yielding clinically insignificant serum levels, at least 50 times less than oral dosing.

Summary of Early Efficacy Testing Patient Experiences

Presented below are a small sample of patient experience reports.

Case #1

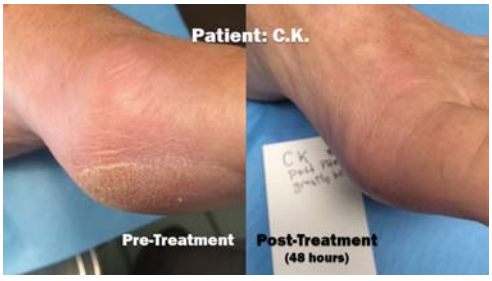
B.G. is a 61-year-old white male who is an admitted alcoholic and has had gout flares in both feet and knees many times. Pedal pulse present bilaterally, skin and nails dystrophic, xerotic and neglected. He is a technician and has been employed for 40 years. He denies allergies and diabetes. He is un-kept and rarely sees doctors. The last 4 days he has acute painful LEFT foot 1st mpj area. It is red and swollen and hot. The patient was sent for uric acid, SMA-12 and CBC. He takes "pain meds" daily. Dispensed ColciGel® with proper instructions. Photos of foot taken. Advised rest, diet modification, elevation of left foot and discussed alcohol intake issues. Requested patient return in 48 hours.



Patient returned 48 hours. 90% improved. Very satisfied. Never got bloodwork. Clinically, greatly improved.

Case #2

C.K is a 49-year-old white male, waiter by trade, East Hampton, NY. Patient is single, denies diabetes or allergies, no recent hospital admissions. Patient reports that he takes no medications. History of Right Achilles tendon partial tear, no surgery. Has good pulses bilaterally, skin and nails normal. However, Left 1st mpj area hot and painful, swollen and red, 2 weeks duration. Symptoms worse now, patient admits he drinks "a lot of beer". Photo taken, patient sent for SMA-12, CBC and uric acid. Dispensed ColciGel® and provided instructions regarding diet



and ColciGel® application. Advised patient to rest, avoid wearing shoe, elevate affected foot, and to return to office in 48 hours.

Patient returned 48 hours. Uric acid from lab 7.7. Patient reports foot pain is more than 50% better and is ambulating well. Patient instructed to continue ColciGel®.

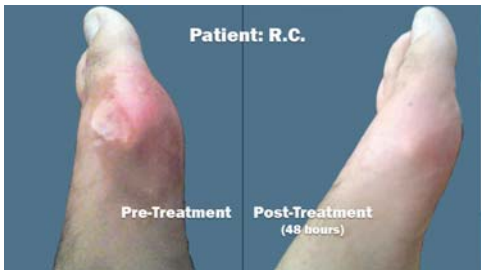
Case #3

E.K is an 88-year-old white female. She was seen with chief complaints of a partial LEFT 1st mpj area that is hot and swollen. Also her dorsum and same foot is edematous. She denies meds and has no known diabetes, nor allergies. No recent hospital admissions and apparently in good health. She admits to daily alcohol and martinis several times daily, recently. X-rays were taken to R/O fracture of metatarsal area, then sent for blood work up, including SMA-12, CBC and uric acid. Post Op shoe for both feet dispensed and instructions for diet modification and limited alcohol. Patient advised to rest and elevate left foot. ColciGel® dispensed along with instructions of use. Photos taken. Patient advised to return in 48 hours.

Patient returned in 48 hours. Patient reports her foot is 95% improved. Patient advised to continue ColciGel®. Very satisfied patient. Uric acid from lab 7.2.

Case #4

Patient R.C. is a 62-year-old male patient with a history significant for Hypertension (controlled) and Gout (since age 32). Patient states he has experienced more frequent flare-ups lately, after increasing his Allopurinol to 300 P.O. q.HS. He controls his acute episodes of gout with oral Colchicine, but reports experiencing severe side effects (Nausea and diarrhea).



Patient presents with an acute flare-up of his gout, affecting his 1st metatarsal phalange joint of the left foot, with swelling, pain, and very limited Range of Motion (ROM). According to him, pain was 9 from a scale of 1-10. He was instructed to apply ColciGel® .75 mL (3 pumps) and wait for results. In about 1 hour, patient R.C. reported improvement of symptoms, 65 % within 1 hour. Then he reapplied another 3 pumps (.75 mL), showing in about 1 hour, 95 % improvement of swelling, pain and ROM in the area of flare-up. After 2 hours, he reapplied another 3 pumps, reporting 95 % relief in the next 4 hours. Then he stopped the medication. He reported no local or systemic side effects and stated preference for this local drug over standard P.O. treatment.

References

1 Khanna,D., Khanna, P., et al. 2012 American College of Rheumatology Guidelines for the Management of Gout. Part 2: Therapy and Anti-Inflammatory Prophylaxis of Acute Gouty Arthritis. Arthritis Care & Research, vol 64; no 10: pp1447-61.

2 FDA Consumer Update, July 9, 2015: www.FDA.Gov/-forconsumers/consumerupdates

3 Terkeltaub, R.A., et al., *High versus low dosing of oral colchicine for early acute gout flare: Twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study*. Arthritis Rheum, 2010. **62**(4): p. 1060-8.

4 Colcrys Package Insert, Takeda Pharmaceuticals USA

5 van Echteld, I., et al., *Colchicine for acute gout (Review)*. Cochrane Collaboration, 2014(8): p. 1-41.

6 Morris, I., G. Varughese, and P. Mattingly, *Colchicine in Gout*. British Medical Journal, 2003. **327**: p. 1275-1276.

7 Borstad, G., et al., *Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis*. Journal of Rheumatology, 2004. **31**: p. 2429-2432.

8 Todd, B., et al., *Assessment of the association between colchicine therapy and serious adverse events*. Pharmacotherapy, 2012. **32**(11): p. 974-980.

9 Terkeltaub, R.A., et al., *Novel evidence-based colchicine dose-reduction algorithm to predict and prevent colchicine toxicity in the presence of cytochrome P450 3A4/P-glycoprotein inhibitors*. Arthritis Rheum, 2011. **63**(8): p. 2226-37.

10 Groff GD, Franck WA, Raddatz DA: *Systemic steroid therapy for acute gout: a clinical trial and review of the literature*. Semin Arthritis Rheum. 1990, **19**: 329-336.

11 Maduri S, Atla VR: *Formulation of Colchicine ointment for the treatment of acute gout*. Singapore Med J 2012 Nov; **53**(11): 750-4

12 Hardevinder Pal Singh, Puneet Utreja: *Elastic liposomal formulation for sustained delivery of colchicine: In Vitro characterization and In Vivo evaluation of anti-gout activity*. AAPS J Vol 11, No 1, March 2009