HEALTH CARE REFORM

The Colchicine Debacle

In 1763, BARON VON STORCK demonstrated that colchicum extract was useful in the treatment of gout. Some 50 years later, an alkaloid was identified from the autumn crocus (*Colchicum autumnale*), which ultimately resulted in the discovery of colchicine. While used in the United States for decades, colchicine, similar to other older drugs, had never been approved with respect to efficacy and safety. The

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Food, Drug, and Cosmetics Act of 1938[1] and its 1962 amendments (Kefauver Harris Amendments) charged the US Food and Drug Administration (FDA) with approving medications based on safety and efficacy. Drugs that entered the market before the passage of the 1938 act or the 1962 amendments to the act, including colchicine, are often referred to as grandfathered drugs. Under the 1962 grandfather clause, a drug was exempted from the effectiveness requirements if its composition and labeling had not changed since 1962 and if it was sold commercially in the United States. While many older drugs without FDA approval claim to be grandfathered, very few marketed drugs are truly entitled to grandfather status because most differ from the previous versions in some respect, such as formulation, dosage or strength, or dosage form. The 1938 act and the 1962 amendments require the FDA to review and approve medications already being marketed; colchicine is one such unapproved product, which has been awaiting FDA approval since 1938.

Several open-label studies suggested the efficacy of colchicine in the treatment of acute gout. However, none were prospective, randomized controlled trials, and they had imprecise criteria for response and inadequate description of research methodology. Considering the lack of sound scientific evidence for the efficacy of colchicine in the treatment of acute gout, the results from these previous studies may have simply represented a natural course of the disease, as opposed to documenting the true efficacy of the drug.

In the 1980s, investigators performed a prospective, randomized controlled trial of colchicine in the treatment of clinically confirmed acute gout.[2] The primary outcome was the percentage of joints demonstrating a 50% decrease in baseline measures of clinical and pain scores. Pain scores were measured using a visual analog scale, while clinical scores used a compounded score including pain, tenderness on palpation, swelling, and redness. At 24 hours, 23% of joints treated with colchicine and 0% of joints treated with placebo had a 50% reduction in clinical scores. In parallel with these results, a 50% reduction in pain scores was observed in 41% of colchicine-treated and 9% of placebo-treated joints. These benefits continued to be observed through 48 hours from the initiation of therapy. All (100%) patients receiving colchicine had gastrointestinal adverse effects (diarrhea and/or vomiting), while 25% of placebo-treated patients reported gastrointestinal effects (nausea but no diarrhea or vomiting). This trial validated the benefit of an inexpensive option for treatment of this common disease.

More than 20 years later, a similar trial was performed,[3] sponsored by URL Pharma. Some methodological differences between the 2 studies included a larger patient population, use of a multicenter study design, and assessment of both low- and high-dose colchicine options in the latter trial. Somewhat similar to the earlier trial, the primary outcome in the latter was a 50% or greater reduction in pain within 24 hours of the first dose of study medication. The results of this investigation mirrored those of the first, with a 32.7% to 37.8% (depending on dose) reduction in pain score of 50% or greater, compared with only 15.5% with placebo. As observed in the earlier investigation, gastrointestinal toxic effects were observed in the majority (76.9%) of patients treated with a high dose but in only 25.7% of patients treated with a low dose; 20.3% of placebo-treated patients reported nausea, vomiting, or diarrhea. An important conclusion of this latter trial was that colchicine could be administered in lower doses with equal efficacy but significantly reduced toxic effects. While the results of this trial conclusively proved that the lower-dose option was equally effective and less toxic, it is important to recognize that the standard of care was evolving toward the use of low-dose colchicine. As an example of this fact, years previously, the European League Against Rheumatism had previously concluded that low-dose, and not high-dose, colchicine should be used for the treatment of acute gout.[4]

The first, somewhat expected, outcome of this latter trial was the FDA subsequently approved the URL Pharma colchicine product (Colcrys) for the treatment of acute gout. However, a number of unanticipated outcomes also ensued. Considering that colchicine previously had never officially been approved for the treatment of acute gout, this FDA approval of the Colcrys product bureaucratically represented a "new" indication for the drug. The US Waxman-Hatch Act[5] mandates that market exclusivity must be awarded to a newly approved drug, and, consequently, the

company was awarded 3 years of market exclusivity. In response, the company subsequently filed suit with the intent of removing all other colchicine competitors from the market. By definition, generic drugs are those evaluated and approved by the FDA to demonstrate equality to a brand-name product. However, these previously marketed colchicine products had never been evaluated and approved by the FDA. Consequently, these products were, from a legal standpoint, "unapproved drugs" and not generic medications, and arguably neither their safety nor efficacy had been established.

In addition to filing suit to remove other colchicine competitors from the market, the manufacturer increased the price of colchicine from what used to be pennies to almost $5 per pill. The result of these actions resulted in a substantially increased cost for patients, third-party payers, and the overall health care system. This increased cost was not isolated to the treatment of acute gout. Colchicine has been used for decades in the treatment of familial Mediterranean fever, a relatively uncommon disease. Consequently, as a result of the Orphan Drug Act,[6] the manufacturer also received 7 years' market exclusivity for the use of Colcrys in the treatment of familial Mediterranean fever. The result of this action was that no generic colchicine could be produced for this extended period.

What are we to conclude from these events? In a previous editorial, Kesselheim and Solomon[7] opine that the colchicine case reveals the limitations of the current system for rewarding innovation by the pharmaceutical industry. Specifically, they conclude that the approval of Colcrys did not result in meaningful improvement in public health. They recommend that approval of costly new agents must be associated with substantial benefit in disease management, an outcome that did not take place with the approval of Colcrys.

Financial incentives, including market exclusivity, are meant to encourage discovery of new molecular entities and bring them to market. While regulatory reward should be a component for pharmaceutical discovery, the case associated with Colcrys reveals a substantial loophole in this system. At least 2 other drugs, guaifenesin and quinine, are marketed, unapproved agents; however, unlike colchicine, these agents do not have as clearly established roles in the treatment of disease. In the future, such benefits, particularly market exclusivity, are far better used for manufacturers of new molecular entities, particularly orphan drugs. The colchicine debacle cannot be repeated.

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EDITOR'S NOTE

Colchicine

The US drug approval system has 2 important goals: getting safe and effective drugs rapidly to patients and rewarding innovation in the pharmaceutical industry by offering market exclusivity for new drugs. Unfortunately, there are weaknesses in our current system, as illustrated by this article concerning colchicine. Offering market exclusivity in the 21st century for a drug that has been used for the treatment of gout since the 18th century, with randomized control trials confirming this benefit from the 1980s, is not in the public service. A system that allows a drug that has been used for gout for centuries to be classified as a new discovery, with a price increase of 500% and generics forced off the market, is not in our patients' interest. Patients have little recourse unless regulations are changed to avoid allowing centuries-old drugs to become a profit-making vehicle for industry at the expense of access to patients.

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