Statins: Is it Safe and Effective to Use Generic “Equivalents”?

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See article by Rahalkar et al., pages xxx-xxx of this issue.

Atorvastatin was the most popular drug prescribed in Canada in 2011 with over 16 million prescriptions filled (including all brand and generic products).1 Although atorvastatin was available in generic form, a strong market persists for the branded product. While Apo-atorvastatin (Apopex Inc, Toronto, ON) was the top selling generic product in 2011 with $156 million in sales, Lipitor (Pfizer Inc, New York, NY), the branded product, still retained CAD$116 million in sales, ranking second for total atorvastatin product sales in 2011. Moreover, although no branded statin product has been shown to be superior to atorvastatin, the top selling individual prescription product in Canada in 2011 was Crestor (AstraZeneca, London, UK)—the only branded statin in Canada without a generic version.2 Clearly, brand name statin products are still being prescribed widely in Canada despite the availability of generic atorvastatin since June 2010.1

Statins are an essential drug therapy, reducing the risk of cardiovascular events by approximately 20% in those with heart disease.3 The release of a generic version of atorvastatin in Canada in June 2010 represented a significant opportunity to improve access to an expensive yet vital medication, with subsequent implications for both population health and cost savings.3 Yet, we can presume a reluctance of prescribers and patients to embrace this switch because we see that use of generic atorvastatin has not been fully adopted. Hesitancy to use generic products is not a new matter.5,6

In this issue of the Canadian Journal of Cardiology, Rahalkar and associates address this issue by reporting on the real world effectiveness of substituting generic for brand name atorvastatin in patients with dyslipidemia.7 This study is important because it addresses a common, practical clinical decision prescribers face every day—whether it is clinically acceptable to use a generic instead of a brand name product—in this case, atorvastatin.

A generic product is a drug that contains the same medicinal ingredients as the original brand name product, but may contain different nonmedicinal ingredients.8 Both brand name and generic drugs are subject to the same safety, quality, and efficacy standards. However, less administrative effort is usually needed for generic drugs compared with brand name drugs in order to receive approval for sale in Canada.7

To prove that their products are safe and effective, generic drug manufacturers must demonstrate that the generic drug performs similarly to the brand name drug in “comparative bioavailability” or bioequivalence studies. Health Canada defines bioequivalence as a “high degree of similarity in the rate and extent of absorption into the systemic circulation of 2 comparable pharmaceutical products in the same dose, that are unlikely to produce clinically relevant differences in therapeutic effects or adverse effects, or both.”9 In bioequivalence studies, the blood level of the drug when given to a small number of healthy human volunteers is usually measured after taking a
single dose of the brand name drug and the new generic drug. The generic drug must show that it delivers the same amount of drug at the same rate as the brand name drug in healthy subjects. Most information about generic products come from these small bioequivalence studies that are required by Health Canada for a generic product to be approved in Canada. However, many clinicians might want information about drug effectiveness in real world patients in order to make clinical decisions.

The study from Rahalkar et al. addresses a concern that some clinicians may harbor about the generic product. A comparison was made between 85 patients with dyslipidemia who were switched from brand name to generic atorvastatin and 143 similar patients continuously prescribed rosuvastatin over the same time period. One of this study’s strengths is its inclusion of actual patients with dyslipidemia instead of healthy male volunteers that are the typical population in bioequivalence studies. Further, nearly 300 patients were studied with at least 1 month of follow-up to assess changes in lipid parameters, whereas bioequivalence studies only require a minimum of 12 subjects, often receiving only 1 dose of medication. Importantly, this is not an outcomes study.

Rahalkar et al. found no difference in the surrogate end points of lipid parameters over time for the atorvastatin intervention group and the rosuvastatin control group. For low-density lipoprotein (LDL), which is generally used as the primary marker for management of dyslipidemia, the average estimate of change in LDL was a nonsignificant increase of 0.32% or 0.059 mmol/L, which most clinicians would not generally consider a clinically meaningful change. Considering that patients receiving atorvastatin had a disruption in their therapy with the generic substitution that could have increased medication noncompliance, the minimal changes found in lipid parameters in this study is reassuring.

By using the data from the study by Rahalkar et al. to calculate the plausible range of changes in LDL using the confidence intervals, we find in the worst case scenario that substitution with generic atorvastatin could increase the LDL by 6.10%, rather than the average estimate of effect of 0.32%, but the best case scenario is that generic substitution may result in a 5.41% further decrease in LDL. Because these differences are modest and may not even make a difference in the risk reduction effect of statins, clinicians and patients have no reason to depart from generic substitution, considering that prescription costs would likely decrease. The more expensive medication should have to prove added value. Although this study provides encouraging results, it does have some limitations. Though its duration was far longer than most bioequivalence studies, it was still short-term at only 1 month. As a retrospective observational study, it is prone to the usual risks of bias, particularly, that there could be competing reasons for no changes in the lipid parameters. However, the authors have attempted to compensate for this by providing a concurrent rosuvastatin comparison group, illustrating similar changes in the outcomes studied. Finally, the study was conducted in a lipid clinic, where there is greater emphasis on managing dyslipidemia and possibly more effort taken to ensure medication adherence. These factors need to be considered when clinicians generalize these findings to their practice setting.

This sole Canadian clinical study on this topic provides further supportive evidence for the interchange of generic atorvastatin for the brand name product without losing the ability to control lipid parameters. Two prior randomized controlled trials conducted in real-world patients in Slovenia and Korea also found similar reductions in LDL between brand and generic atorvastatin products. Evidence from a systematic review of clinical equivalence of head-to-head comparisons of generic and brand name cardiovascular medications provides further evidence that brand name products are not superior for the vast majority of cardiovascular drug classes, including lipid-lowering medications. Studies such as the one by Rahalkar et al. are important in providing reassurance to clinicians about clinical equivalence as they make daily decisions about use of generic atorvastatin in patients with or at risk of cardiovascular disease.

It is unfortunate that few generic products have such real-world evidence to support their effect. What is typical of evaluation of generic preparations is to conduct the standard bioequivalence studies required by Health Canada. To illustrate with atorvastatin, for Apo-atorvastatin, the atorvastatin product with the largest market share in Canada, the approved product monograph reports on the sole study conducted in 17 healthy male volunteers given one 80 mg dose of Apo-atorvastatin and the reference product, Lipitor, in which the 90% confidence intervals around the area under the concentration-time curve ratio ranged from 99.7% to 121.2%—values within the allowable bioequivalence range of 80% to 125% for generic products in Canada. Similar studies are available for each of the other 13 generic atorvastatin products available in Canada.

Given the rudimentary nature of bioequivalence studies, it is not entirely surprising that some prescribers and patients have historically had qualms about using generic versions of medications. The perception of the medical community toward generic medications is often negative as evidenced by the fact that among 43 editorials accompanying publication of these aforementioned cardiovascular clinical equivalence studies, 53% expressed a negative view of generic substitution despite being demonstrated as clinically equivalent. Also, certain patient groups, in particular, low income seniors with low literacy or who are African American mistrust generics more than others.

This issue is not unique to Canada as Health Canada bases its bioequivalence requirements on international standards. However, these standards come with many assumptions. Perhaps the most important assumption that we must explicitly acknowledge is the indirect nature of the bioequivalence end point, and the fact that it is a surrogate end point. It is assumed for oral drugs, that if the blood concentrations of the active ingredient of the generic and brand name drugs are the same, their concentration at the site of action and therefore, their effectiveness will also be the same. By “the same,” there must be no more than a 20% difference between the area under the concentration-time curve and maximum concentration of the brand vs the generic product, which translates into an acceptable ratio at around the 90% confidence interval of each variable of 80% to 125%.

In fact, it is certainly possible that the rate of absorption and excipients within formulations may affect the frequency, onset, and severity of adverse effects, especially in real-world patients with comorbidities. Current knowledge about the effects of excipients on gut wall cytochrome P450 and P-glycoprotein.
activity is limited. It would seem prudent to examine efficacy and toxicity of extensively prescribed generic products in actual patients, particularly for those agents with frequently occurring efficacy or toxicity clinical outcomes that might otherwise go undetected without rigorous evaluation.10

We have an opportunity to harness population-level data to examine clinical outcomes differences between generic and brand name products using postmarketing surveillance.18 The population-based nature and generous sample size of the Canadian Drug Safety and Evaluation Network offers a viable system that could be used to evaluate the most important drugs of widespread use in the population, particularly those with narrower therapeutic margins and those prone to common concentration-dependent adverse effects. When bioequivalence is better established in actual patients, it becomes more apparent that extensive use of generic products would not only reduce health care expenditures but retain therapeutic efficacy. Some measures to increase generic product use include policies for mandatory substitution, tiered formularies, and use of e-prescribing that set the generic product as the default prescription. Effective incentives for physicians to prescribe, pharmacists to dispense, and patients to take generic preparations are often financial. Finally, Canadian generic prices have been considered some of the highest in the developed world. By creating a greater cost differential between brand and generic products, clinicians and patients may be more inclined to make the switch when real-world evidence provides the clinical rationale. Generic medications that have been proven to be safe and effective have an essential role in improving medication access to Canadians while contributing to a sustainable healthcare system.

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