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Simulation of the AUC Changes after Generic Substitution in Patients

To address the debate on the safety of generic substitution quantitatively, the author compared the change in AUC in virtual patients who were simulated for several different scenarios of generic substitution. In four scenarios of original (branded) to generic and generic to generic substitution, 5,000 virtual patients were simulated per scenario using the programming software R. The mean population AUC of generics ranged from 90-110% (scenarios A and B) and 80-123.5% (scenarios C and D) of the AUC of the original. Those patients who had an AUC change (ratio) as a result of drug substitution of less than 0.67 or greater than 1.5 were considered to be in potential danger due to the substitution. We found that less than 6% of patients fell outside of the cutoff range of 0.67-1.5 as a result of original to generic substitution. However, in the case of generic to generic substitution, the proportion was as high as 9-12%. This alerts us to the potential danger of generic substitution, especially for drugs with narrow therapeutic indices.

Key Words : *Therapeutic Equivalency; Generic Substitution; Simulation*

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INTRODUCTION

Since the enactment of the policy of separating prescription and dispensing in Korea in 2000, disputes on generic substitution and generic prescription have not subsided between physicians and the Korean government. In the U.S. and many EU countries, the frequency of generic prescription is known to be higher than 50% of the total number of prescriptions issued. The US FDA has been consistent in maintaining their position that the generics coded as "AB" in the Orange Book of FDA (http://www.fda.gov/cder/ob/default.htm) are therapeutically equivalent without exception, even in the case of drugs with narrow therapeutic indices (NTI) (1). However, the attempt to introduce the individual bioequivalence (BE) in early 2000s seems to reflect serious reconsideration of the current average BE guidance within the FDA, although only a few individual BE study reports had actually been filed. Despite the FDA's official position, physicians have long been raising questions about the efficacy and safety of generics, especially for NTI drugs (2-9).

In this context, the author simulated several scenarios of generic substitution to predict the changes in exposure (area under the drug concentration-time curve; AUC) in 5,000 patients, using the R program (http://www.r-project.org/). The scenarios had different number of generics per original (branded or innovator drug) and different relative bioavailability (BA) in comparison with the original.

MATERIALS AND METHODS

Basic models for the AUC of the original and generics

To simulate the generic substitution, we made several assumptions concerning the AUCs of the original and generic formulations of an active ingredient named Drug X. The first was about the between subject variability (BSV) of the BA (AUC). Because the BSV is related with the difference between each patient's capacity to eliminate drug molecules (i.e., genetic differences in the metabolic activity, individual differences in the GFR, *etc*), it varies with what the active ingredient is, but not with what the manufacturing company is. Therefore, the BSV for Drug X was assumed be normally distributed with the mean value 0 and variance 0.04 (0.2^2) without regard to the formulations. The residual variability (RV) for the original was then assumed to be 10% and the RV for the generics varied between scenarios. The AUCs were assumed to follow log-normal distribution. The following equations summarize these assumptions.

$$\text{Indiv Mean AUC}_{Ori\_i} = \text{Pop Mean AUC}_{Ori}\ (=100) \times \exp(\eta_i),\quad \eta_i \sim N(0, 0.2^2) \quad (1)$$

$$\text{Indiv Mean AUC}_{Gen1\_i} = \text{Pop Mean AUC}_{Gen1} \times \exp(\eta_i) \quad (2\text{-}1)$$

$$\text{Indiv Mean AUC}_{Gen2\_i} = \text{Pop Mean AUC}_{Gen2} \times \exp(\eta_i) \quad (2\text{-}2)$$

In the equation (1), Pop Mean AUC_{Ori} (the mean AUC of the original formulation of Drug X in the patient population), was assumed to be 100 for all scenarios. No units for AUC

were defined throughout the simulation. In the equation (2-1) and (2-2), Pop Mean AUC_{Gen1} and Pop Mean AUC_{Gen2} denote mean population AUCs of two different generics (Gen1 and Gen2). Gen1 and Gen2 are those which are randomly selected from many different generics of Drug X, produced by different companies in each simulation scenario. In equations (1), (2-1) and (2-2), the individual mean AUCs in the i th simulated patient (Indiv Mean AUC_{Ori_i}, Indiv Mean AUC_{Gen1_i} and Indiv Mean AUC_{Gen2_i}) share the same η_i (BSV), which follows a Gaussian distribution of mean 0 and variance 0.04 as mentioned above. Therefore, whatever value the η_i may be, it does not influence the AUC ratios of switched formulations in an individual patient.

Equations (3) and (4) were used to produce the AUC for the i th simulated patient after taking the original (AUC_{Ori_ij}) and generic (AUC_{Gen_i}) formulations of Drug X.

$$AUC_{Ori\_ij}=\text{Indiv Mean } AUC_{Ori\_i}\times(1+\varepsilon_{Ori\_ij}),\ \varepsilon_{Ori\_ij}\sim N(0, 0.1^2) \quad (3)$$

$$AUC_{Gen1\_i}=\text{Indiv Mean } AUC_{Gen1\_i}\times(1+\varepsilon_{Gen1\_i}),\ \varepsilon_{Gen1\_i}\sim N(0, \omega_{Gen1}^2) \quad (4\text{-}1)$$

$$AUC_{Gen2\_i}=\text{Indiv Mean } AUC_{Gen2\_i}\times(1+\varepsilon_{Gen2\_i}),\ \varepsilon_{Gen2\_i}\sim N(0, \omega_{Gen2}^2) \quad (4\text{-}2)$$

Because the simulated patient was assumed to take the original formulation on two separate occasions, the subscript j in equation (3) corresponds to 1 (first time) or 2 (second time). The RV was described using the symbol ε. The ε_{Ori_ij} was assumed to follow Gaussian distribution with mean 0 and variance 0.1^2 (coefficient of variance 10%). In contrast to the original, Gen1 and Gen2, the two different formulations of generics (i.e., manufactured by two different companies) were also assumed to be given to the same virtual patient. The AUC_{Gen} symbols in the above equations were not given the subscript j because they were separately expressed in two different equations, (4-1) and (4-2) by ε_{Gen1_i} and ε_{Gen2_i}. The ε_{Gen1_i} and ε_{Gen2_i} had different variance (ω_{Gen1}^2 and ω_{Gen2}^2, respectively) defined by each scenario. The time intervals between the four events of drug administrations (twice for the original and twice for the generics) per patient were assumed to be long enough to ignore drug accumulation. No period or sequence effect was assumed to exist.

Scenarios

The aim of the simulation was to compare the AUC changes in each patient when he/she was given the original or one of many generics. For all of the four scenarios (A, B, C, and D), the Pop Mean AUC of the original formulation of Drug X was fixed at 100. In scenarios A and B, the Pop Mean AUCs of the generics were 90, 95, 105, and 110, with the RV either being fixed at the same value (10%, scenario A) or being randomly chosen from 1.0, 1.25 or 1.5 times (scenario B) that of the original. More often than not, there may be several tens of generics per original brand in the market. To reflect this, scenario C had 30 generics, with Pop Mean AUC ranging from 80 to 123.5, increasing by a factor of 1.5 but the RVs fixed at 10%. Scenario D had Pop Mean AUCs identical to those of scenario C, but the RV was randomly chosen between 10%, 12.5% and 15% (1.0, 1.25 or 1.5 times that of the original), as in scenario B. The use of larger RV values for the generics compared with that of the original (10%) in scenarios B and D arose from the concern that the quality control services of small-to-medium sized companies producing generics may not be as competent as those practiced in the companies producing the originals. However, the Pop Mean AUC ranges (80-123.5) in scenarios C and D were assumed to satisfy the 90% confidence interval of BE guidances (80-125). The four scenarios are summarized in Table 1.

Data generation

The models and scenarios were simulated using the R program (Version 2.4.1, http://www.r-project.org/). For each virtual patient, two AUCs were simulated after giving the original on two separate occasions (AUC_{Ori_i1} and AUC_{Ori_i2}), and the next two AUCs after giving two different generics (AUC_{Gen1_i} and AUC_{Gen2_i}) which were randomly selected from the generics of each scenario (e.g., selecting two different generics out of 30 generics for scenario C). In other words, four AUC values were generated per patient, who shared the same η_i, but had four different values of ε. The ε which includes intra-subject variability, intra-formulation variability and other unknown errors is changeable at every occasion. This process was repeated 5,000 times per scenario to mimic the situation of prescription and dispensing for the equivalent number of patients.

Table 1. Summary of scenarios A to D

Scenario	Original	Generic		
		Pop Mean AUC	BSV*	RV† (ω_{Gen} value)
A	Pop Mean AUC=100 BSV: $\eta_i\sim N(0, 0.2^2)$ RV: $\varepsilon_{Ori\_ij}\sim N(0, 0.1^2)$	90, 95, 105, 110	Same as original: $\eta_i\sim N(0, 0.2^2)$	0.1
B		90, 95, 105, 110		0.1, 0.125, 0.15
C		80, 81.5, 83, ..., 123.5		0.1
D		80, 81.5, 83, ..., 123.5		0.1, 0.125, 0.15

*Between subject variability (BSV) $\eta\sim N(0, 0.2^2)$; †Residual variability (RV), including the variability coming from within-subject and within-formulation differences. $\varepsilon\sim N(0, \omega^2)$.

RESULTS

Scenarios A to D were sequentially run using the R program. Each run of the scenario constructed data for 5,000 virtual patients and four AUCs (two for the original, two for different generics) were simulated per patient.

AUC ratio of 'Original to Original'

Before assessing the effect of drug switch, the ratio of two original AUCs was calculated for each patient. This was to estimate the fluctuation of the AUC when the same formulation was given to the same patient without any drug switch-in other words, it is a measure of the influence of RV only on the AUC of each patient. In the top panel of Fig. 1, illustrating the results of scenario D, the AUC ratio histogram of 'original to original' ($AUC_{Ori\_i2}/AUC_{Ori\_i1}$, i=1-5,000th patient) is given. The histograms in the other scenarios were almost identical because the model for the original formulation was the same. As shown in the histogram, there were a lot of patients who fell outside of the ratio 0.8-1.25, the equivalence window, in the course of repeated dosing of the original formulation (4.9% of patients were <0.80, 6.2% of patients were >1.25). However, the number of patients who had ratios smaller than 0.67 or greater than 1.5 was negligible. When the same simulation was performed with RV values greater than 10%, the proportion of patients outside of the BE window increased accordingly (data not shown). However, the $AUC_{Ori\_i2}/AUC_{Ori\_i1}$ histogram needs careful interpretation because it indicates the degree of fluctuation of the AUC after each dosing, and not the ultimate increase or decrease in the mean steady state AUC, which stays constant since the patients were given the same original formulation.

AUC ratios of 'Original to Generic'

The AUC ratios ($AUC_{Gen1\_i}/AUC_{Ori\_i1}$) resulting from a switch from the original formulation to a generic in the four scenarios are summarized in Table 2. The two different generics

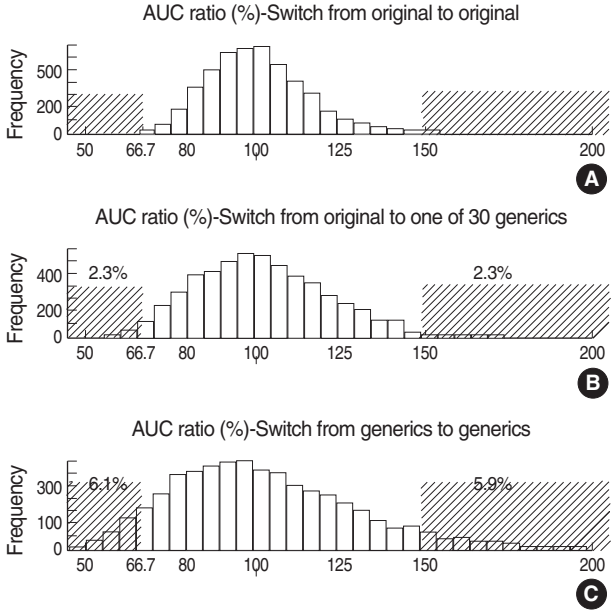

Fig. 1. Simulation results of scenario D, one of the four scenarios. Each histogram represents the AUC ratios of 5,000 virtual patients. The generics in scenario D had a Pop Mean AUC ranging from 80-123.5 (original: 100) and an RV of 10-15% (original: 10%). The proportion of patients falling outside of the ratio margin 0.67-1.5 (shaded zone) was also included. (A) The AUCs fluctuate even when the same patient takes the same original formulation on two occasions because of the RV value, given as 10% in this scenario. (B) $AUC_{Gen1\_i}/AUC_{Ori\_i1}$ in the case of switch from the original to a generic. (C) $AUC_{Gen1\_i}/AUC_{Gen2\_i}$ in the case of switch from a generic to another generic.

Table 2. Simulation results of four scenarios in 5,000 virtual patients. The proportion of patients who had an AUC ratio of less than 0.67 (2/3) or more than 1.5 after switching from 'original to generic' or 'generic to another generic' are given

Scenario	Scenarios-characteristics of the generics on the market: Number of generics onthe market	Pop Mean AUC of generics (original=100)	RV	Simulation results: When switched from original to generic ($AUC_{Gen1\_i}/AUC_{Ori\_i1}$) <0.67	>1.5	Subtotal	When switched from generic to another generic ($AUC_{Gen1\_i}/AUC_{Gen2\_i}$) <0.67	>1.5	Subtotal	Remark
A	4	90-110 (90, 95, 105, 110)	Same as original (10% of mean AUC)	0.6%	0.7%	1.3%	1.4%	1.1%	2.5%	
B	4 (×3)		1, 1.25, 1.5 times original	1.3%	1%	2.3%	2.4%	3.3%	5.7%	
C	30	80-123.5 (even distribution with 1.5 interval)	Same as original (10% of mean AUC)	1.2%	1.8%	3%	4.5%	4.5%	9%	Scenarios C and D may be more like real situation than A and B.
D	30 (×3)		1, 1.25, 1.5 times original	2.3%	2.3%	4.6%	6.1%	5.9%	12%	

RV, residual variability.

given to each patient were randomly selected from those with different Pop Mean AUCs and/or RVs defined in each scenario. An arbitrarily determined safety range of 0.67 (AUC decreased by more than 1/3 after switch) to 1.5 (AUC increased by more than 1.5 times after switch) was used to estimate the proportion of patients who may be harmed by the lack of effect or by overdosing. Along with scenarios A to D, the proportion of those outside of the safety range increased from 1.3% to 4.6%.

AUC ratios of 'Generic to another Generic'

When a patient taking a generic is switched to another generic on the market, what happens to his/her AUC ? To answer to this question, we also simulated the situation of generic to generic switch in each scenario. The proportion of patients who had simulated AUC ratios ($AUC_{Gen1\_i}/AUC_{Gen2\_i}$) outside of the safety range 0.67-1.5 after 'generic to another generic' switch (2.5-12% in different scenarios) were always greater than the above 'original to generic' situation. In scenarios C and D, where the Mean Pop AUC ranges were greater than those for scenarios A and B, there were more patients outside of the safety range, as expected. The results are summarized in Table 2.

DISCUSSION

Disputes on the safety of generic substitution have a long history, with a lot of conflicting reports. Most of the papers addressing the safety problem of generic substitution are case reports on the therapeutic inequivalence caused by substitution. By contrast, the 'pro-substitution' papers have mainly focused on the saving of medication costs in their own countries (10-13), without focusing on the additional costs that may be incurred by therapeutic failure as a result of generic substitution. Richton-Hewett et al. (14), however, measured both the medication cost and healthcare cost after switching branded warfarin to a generic in Boston City Hospital. In their report, the healthcare cost increase from more frequent hospital visits and elongation of the admission period caused by generic substitution was greater than the medication cost saved. Likewise, Hellstrom et al. (15) also showed an increasing number of adverse effects with increasing market shares of generics based on time-series data from 1972 to 1996. If the pharmacokinetic results of generic substitution are to be assessed, well-designed prospective studies are recommended. However, because it is not practical in clinical settings, Rosenbaum et al. (16) detected 20-30% lower phenytoin concentrations in generic formulation-treated patients than in those treated with the original formulation (Dilantin®) via retrospective analysis of the therapeutic drug monitoring data. Against this background, computer simulation is thought to be an appropriate method to predict the changes in drug exposure in a large patient population after generic substitution.

In simulation-based researches, a critical factor is the fidelity or reliability of the model used to perform the simulation. In our model, the distribution of Pop Mean AUC of generics had the strongest influence on the AUC ratios. There are typically several tens of generics per original brand on the market. It is impossible to know their mean AUC values and variance. BE study reports that contain such information are archived by companies and regulatory authorities but these are not to be publicized. Hence, the BSV of 20% and the RV of 10-15% used in the present study were chosen for the convenience of simulation without regard to real BE data. However, the BSV does not influence the switch results as mentioned in the method section. When compared with the author's experiences in several repeated-dosing PK studies, the RV of 10-15% used herein may be a conservative condition, i.e. switch results in the real world may be worse than the simulated ones in this report.

The AUC ratio histograms obtained by the simulation were influenced by both the Pop Mean AUCs and their variability (BSV and RV), as expected. In the model assumption, scenarios C and D were given a broader range of Pop Mean AUC (80-123.5) for the generics compared with scenarios A and B. The shape of the Pop Mean AUC distribution was assumed to be uniform (evenly distributed) with an interval of 1.5 in scenarios C and D. The condition of uniform distribution assumed herein may seem to be 'unfair' for the generic drugs, since the estimate of the mean AUC ratio, which is equivalent to the Pop Mean AUC for the generics in this report, is known to be log-normally distributed with a 90% confidence interval within the 80-125% range, but not uniform-distributed. However, at the same time, none of the scenarios in this report had Pop Mean AUC values of the generics outside of the 80-125% range, a situation which may occur with a probability of less than 10% (tails on both sides of the distribution curve) in the case of 'log-normal distribution'. Therefore, the assumption of uniform distribution was not an unduly harsh condition to make the AUC changes after generic switch seem worse than they really are.

The safety range of the AUC ratio (0.67 to 1.5) used in this study to estimate the proportion of patients falling outside of this range was determined to help the readers to interpret the AUC differences caused by switch. Although the limits of 0.67 and 1.5 may be somewhat arbitrary, the proportion outside of the cutoff range helps us to estimate the possibility of therapeutic failure, especially for NTI drugs. In scenarios C and D, it may be concluded that roughly 10% of patients may experience therapeutic failure when substituted from one generic to another generic. Currently, not a country requests BE studies comparing a generic with another generic, where mean AUC and Cmax may differ by 45% in the most extreme case (80% generic versus 125% generic). This is why the 'generic to another generic' switch was found more dangerous than the 'original to generic' switch in this simulation study.

As with the simulation results herein, it is worth considering the surveys from patients who were exposed to generic substitution (from the original). In Norway, 36% of the patients had one or more negative experiences after switch (17). In Denmark, 6% of patients responded that he/she had experienced more side-effects from the substituted medicine, and 10% felt that the substituted medicine had had a weaker effect, although 85% of responders were positive about the substitution policy itself (18). In Germany, 37% of patients were skeptical towards generics because of their lower price (19). Such concerns will be considerably amplified in Korea, where a substantial proportion of marketed generics are suspected to be of sub-standard quality.

The problem of therapeutic inequivalence may be more serious in those generics approved without BE tests. In many countries, digestives, topical agents (creams, ointments *etc*.) and other parenteral formulations are approved without human PK studies. A case report of therapeutic failure by a generic digestive followed by recovery after switch to the original formulation (20) demonstrates that the therapeutic inequivalence is not simply a theoretical possibility. The fact that 10 generic acyclovir creams were found to have a bioavailability of less than 50% of that of the original formulation in in vitro skin permeation experiments (21) also demonstrates the need to tighten the regulatory web on the topical generics approved without BE tests. Moreover, the quality of intravenous formulations also needs thorough examination to assure their safety and quality. This necessity seems to be greater for some macromolecule drugs, which tend to be harder to synthesize and eliminate detrimental byproducts during the manufacturing process.

Generic prescription or substitution has been widely practiced in the US and EU countries for the purpose of healthcare cost containment. In Ontario, Canada, mandatory generic substitution-a more decisive policy of giving patients generic drugs, regardless of the prescription-was introduced in 2003 (22). In 2007, however, it was reported that the proportion of switching back to the original was higher for antiepileptic agents, one of typical NTI drugs, than for other drugs. Although the causes of switching back were not known, this report implies that the safety and effect of generic substitution of NTI drugs may not be guaranteed under mandatory generic substitution. The perspectives of pharmacists may be different, but they are unlikely to be free from concerns about the safety of patients either. In France, where generic substitution has been possible since 1999, pharmacists are satisfied with the fact that they can exercise the 'substitution right' (23). However, only 42.5% of them were found to dispense generics to patients routinely, and 55% did so to specific patients only (23) for many reasons including safety concerns. A survey report from the US showing that many pharmacists have negative opinions on the generic warfarin substitution (24) is another example showing that pharmacists are also concerned for the safety of NTI generics.

Through this simulation study, we were able to find that a significant proportion of patients may be exposed to the possibility of under-treatment or overdosing by the switch of drugs, especially when switched from a generic to another generic. In conclusion, the present report supports the old notion that prescription drugs-especially the NTI drugs-should be carefully chosen by physicians based on the consideration of individual patient's condition, not by the governmental policy to save medication cost.

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