Citation: Clin Transl Sci (2017) 10, 217–224; doi:10.1111/cts.12442

ARTICLE

Therapeutic Differences in 24-h Ambulatory Blood Pressures in Patients Switched Between Bioequivalent Nifedipine Osmotic Systems With Differing Delivery Technologies

PT Pollak[1,*], RJ Herman[1] and RD Feldman[2]

Comparing modified-release formulations can be difficult using current bioequivalence criteria. Two 60-mg-once-daily nifedipine formulations are deemed bioequivalent in Canada. This study examined the validity of the assumption that these interchangeable, but different, delivery technologies are therapeutically equivalent in maintaining systolic blood pressure (SBP) control throughout the entire dosing interval. We used 24-h Ambulatory Blood Pressure Monitoring to objectively examine whether formulation switches changed population SBP >2 mmHg (reflecting 6% increased stroke mortality) and in what proportion of patients SBP changed ≥6 mmHg (risking unnecessary therapeutic alterations). When 20 patients, previously receiving 60-mg-once-daily Nifedipine-GITS, were switched to Mylan-Nifedipine-XL, population-mean ± SE 24-h SBP increased 3 ± 1.1 mmHg ($P = 0.0173$) and 8-h nocturnal SBP increased 4 ± 1.6 mmHg ($P = 0.0098$). Thus, interchange of nifedipine formulations can affect therapeutic consistency. These data support existing calls to improve criteria for establishing bioequivalence between formulations employing differing modified-release technologies.
Clin Transl Sci (2017) **10**, 217–224; doi:10.1111/cts.12442; published online on 24 February 2017.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
✔ Debate continues over the adequacy of current criteria for comparing extended-release formulations in bioequivalence studies because examples exist of clinically important differences in therapy occurring between modified-release formulations deemed bioequivalent according to current criteria.

WHAT QUESTION DID THIS STUDY ADDRESS?
✔ Given that bioequivalence is assumed to negate the need for therapeutic adjustments following medication substitution, the current study examined whether differing time-release technologies for two once-daily formulations of nifedipine produced any therapeutic differences over its complete 24-h (12-half-life) dosing interval.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE
✔ This study demonstrated clinically important differences in systolic blood pressure occurred between bioequivalent osmotic release technologies, thus confirming regulatory criteria that assess only total drug absorption for the dosing interval are poorly sensitive to differences in timing of drug release.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE
✔ These results support calls for improvement in current bioequivalence criteria for comparing highly-modified-release drug preparations. Use of partial AUCs has already been proposed as a solution by several regulatory agencies.

Regulatory approval of generic medications helps curb the increasing costs of healthcare. Fundamental to generic approval is bioequivalence. This designation implies that if the release characteristics of a comparator test formulation delivers the same amount of active drug over the same time interval as the original reference product, then "the test product can be expected to have the same therapeutic effects and safety profile as the reference."[1] Clinicians thus assume that switching between bioequivalent products should not require any retitration of medication. This study examined the validity of that assumption in the specific case of switches between two nifedipine formulations that extend drug release over 24 h (12 half-lives).

Bioequivalence examines whether sequential serum drug concentrations, collected from patients receiving each of the test and reference formulations, meet criteria regarding allowable differences in two pharmacokinetic parameters: area under the concentration–time curve (AUC) and maximum concentration (C_{max}). These statistical measures do not represent product performance in any single individual, but rather average performance for the entire study cohort.[2] Beneficially, bioequivalence avoids the need to demonstrate

[1]University of Calgary, Calgary, Alberta, Canada; [2]Memorial University, St John's, Newfoundland & Labrador, Canada. *Correspondence: PT Pollak (amiokinetics@hotmail.com).
Received 13 December 2016; accepted 23 December 2016; published online on 24 February 2017. doi:10.1111/cts.12442

therapeutic equivalence using clinical trials, thus lowering the costs of developing generic medications. It is also the basis upon which pharmacies can justify not alerting healthcare providers when drug formulations are interchanged in their patients.

Bioequivalence criteria were originally developed for comparing immediate-release drug formulations. Although the rationale for producing modified-release formulations is to shift the timing of drug release, current bioequivalence criteria are not directly geared towards examining for differences in time course of drug release.[3] Specifically, no time-based parameters are included to directly evaluate that time course.[1,4,5] This has led to extensive discussions about how to assess bioequivalence between modified-release preparations,[6] and how to deal with other confounders of current criteria used for bioequivalence.[7] Documentation of examples in which current bioequivalence criteria fail to assure clinically equivalent therapy after a medication substitution is important to support initiatives to improve regulatory criteria for comparing modified-release formulations.

The dihydropyridine calcium-channel blocker nifedipine is widely used in the management of hypertension. This class of peripheral vasodilators is characterized by a steep concentration–response curve for blood pressure reduction. Its short 2-h half-life makes nifedipine immediate-release preparations inappropriate as antihypertensive agents. The frequent or continuous administration of small amounts of nifedipine is a requirement to avoid undesirable sympathetic responses to the effects of rapid increases in drug concentration and repeated lapses in the antihypertensive effect when concentrations quickly decline. Therefore, modified-release formulations were developed to provide more sustained delivery of nifedipine. A first-order, prolonged-action tablet was the original formulation of nifedipine successfully approved as an antihypertensive agent. However, introduction of the Gastro-Intestinal Therapeutic System (GITS) further improved the delivery pattern of nifedipine, providing both superior effectiveness and tolerability, by eliminating high peak concentrations, and providing better adherence, by allowing once-daily administration.[8] Thus, nifedipine as an antihypertensive agent is highly dependent on the characteristics of a sophisticated delivery technology, rather than on the molecule itself. The consistency of GITS delivery of nifedipine also produces less tachycardia and sympathetic activation than with even a long-half-life dihydropyridine such as amlodipine.[9] Furthermore, the constant delivery of a short half-life dihydropyridine produces a therapy with rapid equilibration to a temporary steady-state drug concentration in 6–8 h, allowing for more rapid dose titration and discontinuation than agents that rely on long half-life to produce a low fluctuation in serum concentrations.

Numerous outcome trials have documented the safety and effectiveness of the GITS preparation.[10,11] Its push-pull osmotic pump (PPOP) is based on a two-layer technology that conserves propellant in order to produce a zero-order drug delivery profile. Its success prompted the commercial development of the simpler Elementary Osmotic Pump (EOP) by Osmotica Pharmaceuticals (Marietta, GA). EOP is based on an older monolayer osmotic technology described by Theeuwes that produces an extended first-order drug delivery profile.[12] Kremers Urban (Princeton, NJ) uses the EOP technology to produce a once-daily nifedipine marketed as Mylan-Nifedipine-XL in Canada (Mylan Pharmaceuticals, Etobicoke, Ontario, Canada; Nifedipine extended release prescribing information US Rev.9E 07/2014). In Canada, Mylan-Nifedipine-XL (first-order) has been deemed bioequivalent to Nifedipine-GITS (zero-order), based on comparison of cumulative AUC for their complete 24 h (12-half-life) dosing intervals. Being dispensed Mylan-Nifedipine-XL, provides no economic advantage for the patient in Canada, as Nifedipine-GITS is marketed at the same price under the name Adalat XL by Teva Pharmaceuticals (Teva Canada, Toronto, Ontario, Canada).

Figure 1 Similar appearance, differing delivery technologies. Most patients were unaware that substitutions were made by their pharmacies back and forth between Nifedipine-GITS (zero-order delivery) on the left, and Mylan-Nifedipine-XL (first-order delivery) on the right.

Soon after Mylan-Nifedipine-XL (DIN 02321149) was introduced for clinical use in Canada, we observed inexplicable increases in systolic blood pressure (SBP) of $>$10 mmHg in several patients, previously well controlled on Nifedipine-GITS 60 mg.[13] Although the patients denied any change in their medication or adherence to therapy, inquiries to their pharmacies revealed that substitution of their once-daily nifedipine had occurred. In each case, the patients had been unaware of the substitution because of the similarity in appearance of the two formulations (**Figure 1**). Further inquiries revealed that, although the bioequivalent formulations were both oral osmotic pumps, they were in fact using different delivery technologies. Given previous evidence that the rate of drug delivery from the first-order EOP technology waned in the last portion of the dosing interval,[14] there was reason to suspect that clinically important differences could exist between the effects of the two technologies, at least in some patients.

The most ethical way to critically examine for possible differences in antihypertensive effects during the entire dosing interval was to replicate the natural experiment already occurring in the community. While pharmacies were already switching patients between formulations of nifedipine, expected to be interchangeable, a study protocol could

add randomization and recording of the timing and direction of the switch, and 24-h Ambulatory Blood Pressure Monitoring (ABPM) as a tool to objectively document blood pressure over the complete dosing interval, and record any differences occurring after a switch.

METHODS

The primary goal of this study was to examine whether bioequivalence approval under current criteria can always assure that differing extended-release technologies produce clinically equivalent effects over their entire dosing interval. The example chosen was an investigation of the observation that some patients were no longer achieving target blood pressures after being switched between two once-daily nifedipine formulations, deemed to be bioequivalent.

SBP is the hypertension parameter with the largest cardiovascular impact,[15–17] and nifedipine has its biggest effect on SBP.[9] Each 2-mmHg decrease in mean *population* SBP reduces stroke mortality by 6%.[18] Therefore, the logical primary comparison for clinical difference between formulations was to prove whether a change in SBP $>$2 mmHg could be excluded when the study population was switched between formulations. Given that loss of propellant from a first-order EOP delivery system could reduce the rate of delivery at the end of the dosing interval, a secondary comparison was to exclude that a greater separation in SBP occurred during the last 8 h of the dosing interval. Since the majority of patients take their antihypertensive medications with breakfast, the normal nocturnal dip in SBP will occur at the end of the dosing interval. Therefore, ABPM was chosen to allow unbiased examination of the effect of formulation switches over the entire 24-h dosing interval, including nocturnal blood pressure data. Furthermore, ABPM provided an expectation of reproducibility of mean 24-h SBP within $<$1 mmHg on repeat measurements under similar conditions.[19]

Because the clinician treats a patient, not a population, a 2-mmHg population change in SBP is of little interest in daily practice. Therefore, the tertiary goal of this study was to estimate the proportion of the population expected to develop blood pressure differences large enough to potentially cause an alteration in their therapy following nifedipine substitution. Given that adding an ACE inhibitor such as ramipril to an antihypertensive regimen is expected to change SBP by 6 mmHg on average, this value was chosen for modeling risk.[20]

The study protocol received approval from the University of Calgary Health Ethics Review Board. Just as in the community, none of their other therapy was altered as a requirement not to subject the study population to risk of inadequate hypertension control. The only intervention made was to pre-specify the timing and direction of the formulation switches they were already being exposed to through their prescription renewals in the community. Because many of the patients lived more than a 1-h drive from the clinic, travel burden was limited to an enrollment visit and two ABPM studies. Blood work that would be required to repeat previous pharmacokinetic studies was not possible in these uncompensated clinic patients. Written, informed consent was obtained from all subjects, and the study was conducted in accordance with the ethical standards of the University of Calgary Health Ethics Review Board.

Clinical study participants

Male and female patients $\geq$18 years of age with primary hypertension already treated with once-daily 60-mg nifedipine as part of their antihypertensive regimen were approached for consent. Patients with SBP $>$160 mmHg on therapy were excluded.

Safety measures

Safety was monitored by self-reported adverse events. Given that no changes were made to their clinical management (including their previous exposure to both different nifedipine formulations available in the community), only blood pressure was monitored and patients were not exposed to venipuncture for clinical chemistry or drug measurement.

Study design

A sample of 20 patients was chosen to match the cohort size typical of studies conducted in healthy volunteers to establish bioequivalence. Patients on stable therapy for $>$6 weeks were recruited from local specialist clinics. No changes were made to the patients' concomitant medications and other clinical management, with the expectation that no clinically important perturbation in blood pressure should occur after a switch between bioequivalent formulations of a single agent. Although performing an ABPM study the day after each switch would have answered the question regarding therapeutic equivalence, a 14-day acclimatization period (168 half-lives) was used after each switch in order to gauge the practical effect of switching formulations. Thus, blood pressure data, if anything, underestimated any acute therapeutic differences that might have occurred the day after drug substitution.

A crossover design allowed each patient to serve as their own control. Randomization of the switching sequence within balanced blocks of four subjects allowed examination for any period effect related to direction of switching using a sequence term in an analysis of variance (ANOVA). The direction of switches between the 60-mg formulations was randomized to either: Sequence A, receiving Nifedipine-GITS for 2 weeks, then Mylan-Nifedipine-XL for 2 weeks; or Sequence B, receiving Mylan-Nifedipine-XL for 2 weeks, followed by Nifedipine-GITS for 2 weeks. The study timeline is depicted in **Figure 2**.

Fourteen days before the first ABPM recording, a limited examination was performed in order to document vital signs and ensure that patients were not suffering any acute intercurrent illness. All subjects were instructed to take their nifedipine at $\sim$07:00 a.m. to standardize administration time. All ABPM devices (Spacelabs model 90207, Spacelabs Healthcare, Mississauga, ON, Canada) were validated against a mercury manometer using a three-way stopcock as per the Spacelabs manual.

Patients were asked to arrive at the clinic in the early morning. Following documentation of SBP, diastolic blood pressure (DBP) and heart rate (HR) by the study physician, an ABPM device was attached and operation of the machine reviewed with the patient. Correct function of the

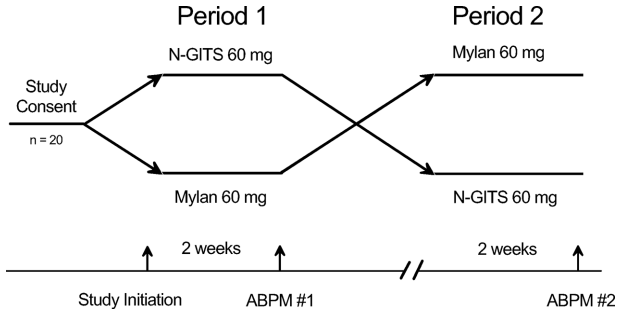

Figure 2 Flowchart of treatment assignment and timing of ambulatory blood pressure monitor (ABPM) assessments. Vertical arrows mark time of study initiation and ABPM measurements for either Mylan-Nifedipine-XL (Mylan) or Nifedipine-GITS (N-GITS).

device was confirmed by observing two successful readings. Each patient was studied with the same machine in both study periods. Adherence to therapy was assessed using pill counts. Each ABPM study produced 64 observations consisting of 48 readings taken every 20 min from 06:00 to 22:00, and 16 readings taken every 30 min from 22:00 to 06:00. A standard report, providing mean values for both 24-h and 8-h nocturnal (22:00 to 06:00) time periods, was generated by the Spacelabs software (Spacelabs Ambulatory Blood Pressure Report Management System v. 3.0.1.4). An additional comma-separated values (.csv) file containing the raw monitoring values for each parameter was generated for each patient.

Statistical analysis

Although SBP was the primary outcome measure, plots of mean 24-h curves for each of SBP, DBP, and HR were examined for effects of switching formulations in the population. A paired ANOVA was used to compare mean 24-h SBP, DBP, and HR between the two periods of the crossover. Effects on the terminal portion of the 24-h dosing interval (22:00 to 6:00) were also compared using a paired ANOVA.

Following conventional ANOVA, a Generalized Additive Mixed Model (GAMM) was used to examine the raw data.[21] All GAMM analyses were conducted using the "mgcv" package in R statistical software.[22] The number of terms included in the model was optimized using the Akaike Information Criteria (AIC). In this way, all 2,560 readings collected for each parameter during the study were considered simultaneously, maximizing efficiency of data use. Period effect was again ruled out using a model term for sequence A vs. B. Once the 24-h course of SBP curves best fitting the population were predicted by GAMM from all the data for each formulation, R software compared the intercepts of the fits in a fashion analogous to comparing slopes and intercepts in a linear regression analysis. For all analyses, $P < 0.05$ was accepted as statistically significant.

Limitations

The nature of both the dosage form and the patients required an open-label study. To function as designed, these pumps cannot be overcoated or have their semipermeable shells altered. Observed, early morning dosing of blindfolded patients for >28 days was neither practical nor ethical, given driving distances. However, lack of blinding was mitigated by the use of ABPM, a technique known to be difficult to bias and shown to be suitable for open-label studies.[23] Furthermore, patients seldom recognized the difference in the medication they were receiving due to their similar external appearance (**Figure 1**).

Table 1 Subject demographics

Parameter	10 Males	10 Females	All subj.
Mean Age (y)	63.2	65.2	64.2
Mean BMI (kg/m^2)	30.6	31.8	31.2
Mean Weight (kg)	95	84	89
Mean Height (cm)	176	163	169
Mean Baseline systolic (mmHg)	133	144	138
Mean Baseline diastolic (mmHg)	80	84	82
Mean Baseline heart rate (bpm)	67	75	71
Numbers of Patients with:			
D_x Hypertension	10	10	20
> 2 Antihypertensive Agents	9	5	14
ACE/ARB	9	9	18
Thiazide	6	8	14
Statin	4	6	10
ASA	5	2	7
D_x Atrial Fibrillation	3	4	7
Amiodarone	3	4	7
Anticoagulation	1	5	6
D_x Coronary Vascular Disease	0	3	3
D_x Obstructive Sleep Apnea	3	3	6
D_x Diabetes	3	4	7
D_x Smoker in last 2 y	0	0	0

D_x = Diagnosis of…

Results

All 20 subjects completed both treatment periods, having received each formulation of nifedipine in a randomly assigned order. **Table 1** confirms that their demographic profile is typical of patients with moderate hypertension, often having effects of hypertension such as atrial fibrillation, and as in major outcome trials, usually requiring multiple agents to achieve blood pressure targets.[24] Pill counts showed adherence to medication was complete. The order in which the crossover occurred did not affect results, as no period effect was detected.

Figure 3 plots mean SBP, DBP, and HR for the 20 subjects at each of the 64 measurement points over 24-h fit by local regression in R. As expected,[9] the magnitude of effect on DBP was less than that on SBP, and nifedipine delivered by osmotic release technology did not affect HR. Mean DBP was not statistically different between formulations by ANOVA, but did follow the same pattern of increasing separation over the dosing interval as seen with SBP. Mean 24-h HR was 64 bpm with either formulation and varied by only 15 bpm.

SBP follows the bimodal circadian undulation typically seen in 24-h ABPM studies.[25] Paired ANOVA for repeated measures showed both mean 24-h and terminal 8-h SBP to be higher when subjects were receiving the

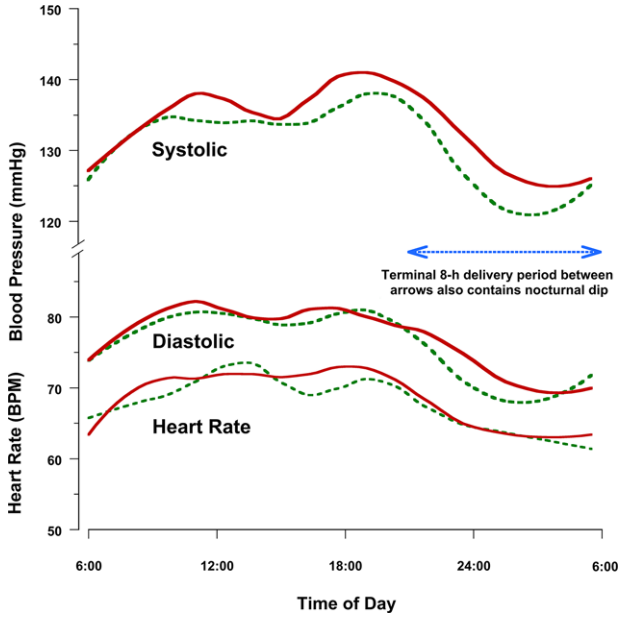

Figure 3 Curves for ABPM data plotted using the local regression LOESS function in R statistical software. Readings from 64 time-points over 24 h for systolic and diastolic blood pressure (SBP and DBP) and heart rate (HR) provided 2,560 values for each parameter from 20 patients over two study periods. Solid-red lines represent data fit from Mylan-Nifedipine-XL. Dashed-green lines represent data fit from Nifedipine-GITS. SBP curves for two patients are statistically different and continue to further separate during the terminal 8 h (nocturnal period) of the dosing interval, as delivery from Mylan-Nifedipine-XL is predicted to decline in a first-order pattern. DBP curves follow a similar pattern, but are less affected by action of dihydropyridines and were not statistically different. HR remains clinically unaffected by constant, low-rate delivery of nifedipine, varying by only 15 bpm over the course of the day.

Table 2 Systolic blood pressures reported by Ambulatory Blood Pressure Monitor for 20 patients when treated with Nifedipine-GITS vs. Mylan-Nifedipine-XL

	24-h Mean SBP			Nocturnal 8-h Mean SBP	
Subj. #	**N-GITS**	**Mylan-N**		**N-GITS**	**Mylan-N**
1	140	140		126	128
2	137	148		135	143
3	132	133		127	130
4	139	147		129	138
5	134	134		132	129
6	152	151		153	148
7	125	130		116	130
8	134	142		129	140
9	139	137		127	130
10	122	129		103	115
11	128	130		134	127
12	160	155		141	134
13	127	131		113	131
14	128	131		122	133
15	130	125		127	117
16	140	141		133	134
17	121	118		116	114
18	114	119		99	108
19	127	134		120	129
20	124	125		116	118
Mean	133	135	Mean	125	129
SE	2.4	2.3	SE	2.8	2.3
P	0.030		*P*	0.039	

SBP, Systolic Blood Pressure; N-GITS, Nifedipine-GITS; Mylan-N, Mylan-Nifedipine-XL.

Mylan-Nifedipine-XL formulation, with the differences being greater during the latter part of the dosing interval (**Table 2**). Mean ± SE for 24-h SBP reading was 133 ± 2.4 mmHg when patients received Nifedipine-GITS and 135 ± 2.3 mmHg ($P = 0.030$) when they received Mylan-Nifedipine-XL. The respective mean nocturnal 8-h readings were 125 ± 2.8 mmHg and 129 ± 2.3 mmHg ($P = 0.039$).

A GAMM used to more efficiently fit all the raw SBP data for the study population generated the plots for each formulation seen in **Figure 4**. Mean ± SE 24-h SBP predicted by the GAMM model for patients while receiving Nifedipine-GITS was 132 ± 2.7 mmHg, very similar to the average of 24-h SBP reported by the Spacelabs analytical software. When the same patients were receiving Mylan-Nifedipine-XL, mean ± SE 24-h SBP predicted by GAMM was 3 ± 1.1 mmHg higher ($P = 0.0173$). Modeling only the nocturnal 8-h SBP showed SBP to be 123 ± 3.1 mmHg for the last portion of the dosing interval when patients were receiving Nifedipine-GITS. When the same patients were receiving Mylan-Nifedipine-XL, SBP was 4 ± 1.6 mmHg higher ($P = 0.0098$).

The likelihood of a given patient experiencing a clinically important change in SBP (>6 mmHg) following a switch between the two 60-mg formulations of nifedipine was quantified using a Monte Carlo simulation. Parameters estimated from the GAMM analysis where used to simulate 10,000

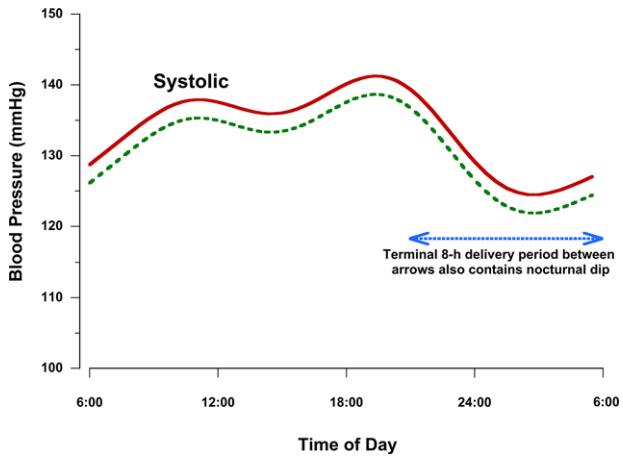

Figure 4 Plots of mixed-effects fit of SBP data over time using GAMM function in R statistical software. Solid-red lines represent data fit from Mylan-Nifedipine-XL. Dashed-green lines represent data fit from Nifedipine-GITS. There is a clear, statistically significant separation of 3 ± 1.1 mmHg ($P = 0.0173$) between the curves of best population fit for each formulation, which was even larger during the last 8 h of the dosing interval.

patient-drug switches. Switch from Nifedipine-GITS to the alternate Mylan-Nifedipine-XL formulation was associated with a 23% risk mean 24-h SBP increasing by >6 mmHg and a 39% likelihood of an increase >6 mmHg during the nocturnal dip that occurred in the last 8 h of the dosing interval.

Discussion

Bioequivilence is a valuable tool in providing medications at lower costs. However, under some circumstances concerns have been raised about the ability of current criteria to reliably evaluate drug delivery from highly-modified-release formulations. This study was inspired by clinical observation that several patients developed differing blood pressures when switched between bioequivalent once-daily nifedipine formulations. On a population basis, long-term differences in hypertension control, as little as 2 mmHg of SBP are associated with effects on both morbidity and mortality outcomes.[18,26–28] Even a few months of suboptimal blood pressure control adversely affected outcomes in the ASCOT and VALUE trials.[29,30] However, for the individual patient the important question is how likely are such blood pressure changes to inspire their clinician to alter their therapy. As patients are often switched back and forth between the two equally priced nifedipine formulations, the risk of unnecessary alteration in therapy arises every few months when they refill their prescriptions.

This study demonstrated that, while both zero-order and first-order nifedipine delivery (GITS vs. EOP) can provide blood pressure control, many patients experience clinically important differences in therapeutic responses between formulations. The design difference between GITS and EOP is based on how their propellants are incorporated. GITS consists of an osmotic polysaccharide layer sandwiched against a nifedipine wafer. Once the tablet is encapsulated in a semipermeable shell, a delivery orifice is laser-drilled on the nifedipine side of the tablet. Following ingestion, hydration dissolves the nifedipine, which is then extruded out the orifice with a consistent delivery, as the polysaccharide layer expands at a constant rate.[10] Without access to the orifice, there is no loss of propellant, and the rate of nifedipine release remains the same per unit of time (zero-order). This maintains consistent circulating nifedipine concentrations throughout the complete dosing interval.[31] In contrast, loss of propellant is intrinsic to the design of the EOP tablet in which an osmotic polysaccharide is intermixed with the active drug inside its semipermeable shell. Both components are simultaneously expelled, producing a slow (first-order) decline in drug delivery throughout its gastrointestinal transit.

Although first-order delivery technology can be optimized to approximate zero-order delivery over some portion of the 24-h dosing interval by adjusting the propellant, orifice size, and shell composition,[32] it is pharmacokinetically impossible to exactly replicate zero-order delivery. *In vitro* dissolution profiles confirm a greater decline in drug delivery at the end of the dosing interval with EOP compared with GITS.[14] Food also caused a greater perturbation of EOP drug release than with GITS. Overall, the plateau phase of plasma drug concentrations was 6 h shorter for EOP than the 20 h observed with GITS. Indeed, the greatest discrepancies in SBP that were observed in this study occurred during the last third of the dosing interval, when the rate of drug release from the EOP formulation slowly wanes. The steep concentration–response curve for nifedipine means that even small lapses in maintenance of concentrations has measurable effects on blood pressure.[33]

The 60-mg dosage of nifedipine is a highly effective long-acting antihypertensive agent. However, the inherent half-life of nifedipine remains 2 h, irrespective of its release profile, absorption pattern, or dosing interval. Therefore, nifedipine concentrations are rapidly sensitive to any change in rate of drug release over as little as one-twelfth of the 24-h dosing interval. Thus, even though, in general, they appear to be equivalent dosing forms,[1,4,5] differing orders of nifedipine delivery technology do make the two oral, osmotic, controlled-release, once-daily nifedipine formulations different.

For immediate-release preparations, AUC and C_{max} succinctly characterize a drug's release profile. However, when timing of release is not determined by first-order dissolution, these criteria may no longer reliably describe that release profile. Therefore, comparing partial AUCs over the dosing interval has been proposed to better characterize timing of release.[34] In fact, the US Food and Drug Administration (FDA) guidance now recommends partial AUCs as a way to compare late release of drug from formulations with differing release mechanisms,[35] and subject-by-formulation interaction analyses have been suggested to characterize variations in patient responses to switching formulations.[36]

In bioequivalence studies, differences in timing of nifedipine release from these formulations are masked by only comparing cumulative AUC for the total 12-half-lives of the 24-h dosing interval. Even if AUC were exactly the same for each formulation for 10 out of 12 half-lives, but drug delivery from one formulation fell to zero for only 2 half-lives, the effect on AUC for the dosing interval would be only 16%. However, blood pressure control would clearly lapse for that part of the day. Indeed, this study showed increasing separation of blood pressure responses between formulations over the dosing interval. This suggests EOP provides declining concentrations at the end of the dosing interval, yet that difference did not trigger failure of bioequivalence standards using current AUC criteria.

Thus, the differences in clinical effects between the two formulations observed in this study do support calls for changes in the regulatory criteria for determining bioequivalence between highly-modified-release formulations. Indeed, partial AUCs would have been able to detect any difference in nifedipine concentrations during the latter part of the dosing interval.

In conclusion, the observation of blood pressure differences in patients being switched between Nifedipine-GITS and Mylan-Nifedipine-XL suggests that concerns about the adequacy of using current bioequivalence criteria to assess highly-modified-release formulations have a real foundation. Despite their bioequivalent designation, switching these formulations caused a clinically meaningful change in population blood pressure. Although, a shift in population SBP of 2 mmHg would have clinically important

epidemiological effects, each individual patient will respond differently to medication switches. Adequacy of nocturnal dipping appears to be an even more important predictor of outcomes than daytime blood pressure.[37,38] Given that the majority of patients favor morning dosing and nocturnal dipping is occurring at the end of their dosing interval, this is a concern that bears further study.

More important for the individual patient is the possibility of therapeutic inconsistency when switched back and forth between nifedipine formulations, leading to detrimental adjustments in their antihypertensive therapy. It appears that 23% of the time, pharmacy switches of nifedipine formulations will alter SBP sufficiently to stimulate consideration of antihypertensive regimen adjustment. Since the potential for switching occurs every 1–3 months, the result could be a frustrating inability to achieve stable blood pressure control. Although ABPM could be used to assess the effects of a nifedipine switch in any given patient, because the two formulations are sold for the same price in Canada, the cost of such clinical assessment would not be justified. Therefore, to achieve consistent care, the simple, logical recommendation would be to preclude the interchange of these equally priced formulations. Remaining on one formulation or the other would be cost-neutral and assure consistency of therapy, a win-win for the patient. At the very least, when a clinician detects an unexplained blood pressure change in a patient receiving nifedipine, they should be aware to ask whether the patient has recently refilled their prescription, since the patient will likely be unaware of any specific switch in nifedipine formulation.

Acknowledgments. The authors thank Navdeep Dehar for her help in recruitment and gathering blood pressure data, Mingkai Pen for his skilled use of R statistical software, and Corey Toal for his thoughtful review and comments on the article.

Author Contributions. P.T.P., R.J.H., and R.D.F. wrote the article; P.T.P. and R.J.H. designed the research; PTP performed the research; P.T.P., R.J.H., and R.D.F. analyzed the data.

Conflict Of Interest/Dislosure. The completed study protocol was submitted to an international funding competition for financial support and was awarded an Investigator Sponsored Study (ISS) Grant. The ISS Grant competition is supported at arm's length by Bayer Inc., who played no role in the protocol design, study execution, or analysis and interpretation of the findings. P.T.P. has received speaking honoraria from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Forest Laboratories, and Servier. R.J.H. has none declared. R.D.F. has received honoraria from Bayer, Servier, and Valeant.

1. Health Canada. Guidance document: Conduct and analysis of comparative bioavailability studies. File number: 12-105972-31 [Internet]. 2016 [updated 22 May, 2012; cited 20 Apr, 2016]. Available from: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/bio/gd_cbs_ebc_ld-eng.php
2. Canadian Agency for Drugs and Technologies in Health (CADTH). What are bioavailability and bioequivalence. [Internet]. 2016 [updated 11 Dec 2011; cited 20 Apr 2016]. Available from: https://www.cadth.ca/media/pdf/Generic_prof_supplement_en.pdf
3. Pollak, P.T., Freeman, D.J. & Carruthers, S.G. Mean apical concentration and duration in the comparative bioavailability of slowly absorbed and eliminated drug preparations. *J. Pharm. Sci.* **77**, 477–480 (1988).
4. European Agency for the Evaluation of Medicinal Products Human Medicines Evaluation Unit. Note for guidance on modified release oral and transdermal dosage forms: Section II (Pharmacokinetic and clinical evaluation) [Internet]. 2016 [updated 28 July 1999; cited 20 April 2016]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003126.pdf
5. European Medicines Agency. Guideline on the investigation of bioequivalence [Internet]. [updated 20 Jan 2010; cited 20 Apr 2016]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf
6. Endrenyi, L. & Tothfalusi, L. Metrics for the evaluation of bioequivalence of modified-release formulations. *AAPS J.* **14**, 813–819 (2012).
7. Burmeister Getz, E., Carroll, K.J., Jones, B. & Benet, L.Z. Batch-to-batch pharmacokinetic variability confounds current bioequivalence regulations: A dry powder inhaler randomized clinical trial. *Clin. Pharmacol. Ther.* **100**, 223–231 (2016).
8. Swanson, D.R., Barclay, B.L., Wong, P.S. & Theeuwes, F. Nifedipine gastrointestinal therapeutic system. *Am. J. Med.* **83**, 3–9 (1987).
9. de Champlain, J. *et al.* Different effects of nifedipine and amlodipine on circulating catecholamine levels in essential hypertensive patients. *J. Hypertens.* **16**, 1357–1369 (1998).
10. Brown, M.J. *et al.* Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet.* **356**, 366–372 (2000).
11. Poole-Wilson, P.A. *et al.* Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. *Lancet.* **364**, 849–857 (2004).
12. Theeuwes, F. Elementary osmotic pump. *J. Pharm. Sci.* **64**, 1987–1991 (1975).
13. Pollak, P.T. Therapeutically relevant blood pressure differences with two nifedipine (60 mg) osmotic delivery systems of differing design: three case reports. *Int. J. Clin. Pharmacol. Ther.* **48**, 400–404 (2010).
14. Anschutz, M. *et al.* Differences in bioavailability between 60 mg of nifedipine osmotic push-pull systems after fasted and fed administration. *Int. J. Clin. Pharmacol. Ther.* **48**, 158–170 (2010).
15. Black, H.R. The paradigm has shifted, to systolic blood pressure. *Hypertension.* **34**, 386–387 (1999).
16. Mancia, G., Seravalle, G. & Grassi, G. Systolic blood pressure: an underestimated cardiovascular risk factor. *J. Hypertens. Suppl.* **20**, S21–S27 (2002).
17. Strandberg, T.E. & Pitkala, K. What is the most important component of blood pressure: systolic, diastolic or pulse pressure? *Curr. Opin. Nephrol. Hypertens.* **12**, 293–297 (2003).
18. Stamler, R. Implications of the INTERSALT study. *Hypertension.* **17**, I16–I20 (1991).
19. Palatini, P. *et al.* Factors affecting ambulatory blood pressure reproducibility. Results of the HARVEST Trial. Hypertension and Ambulatory Recording Venetia Study. *Hypertension.* **23**, 211–216 (1994).
20. McCarron, D. 24-h blood pressure profiles in hypertensive patients administered ramipril or placebo once daily: magnitude and duration of antihypertensive effects. Ramipril Multicenter Study Group. *Clin. Cardiol.* **14**, 737–742 (1991).
21. Wood, S. Generalized Additive Models: An Introduction with R. Publisher: CRC Press, Boca Raton, FL. Short Title: Generalized Additive Models: An Introduction with R. ISBN: 9781420010404. 2006.
22. R Core Team. R: A language and environment for statistical computing. [Internet]. 2016 [updated 14 Apr 2016; cited 20 Apr 2016]. Available from: http://www.R-project.org
23. Parati, G. & Staessen, J.A. Hypertension drug trials based on ambulatory blood pressure monitoring: when is a double-blind controlled design needed? *J. Hypertens.* **21**, 1237–1239 (2003).
24. Haller, H. Effective management of hypertension with dihydropyridine calcium channel blocker-based combination therapy in patients at high cardiovascular risk. *Int. J. Clin. Pract.* **62**, 781–790 (2008).
25. Tikkanen, I. *et al.* Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension. *Diabetes Care.* **38**, 420–428 (2015).
26. Whelton, P.K. *et al.* Primary prevention of hypertension: clinical and public health advisory from The National High Blood Pressure Education Program. *JAMA.* **288**, 1882–1888 (2002).
27. Turnbull, F. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet.* **362**, 1527–1535 (2003).
28. Lewington, S., Clarke, R., Qizilbash, N., Peto, R. & Collins, R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* **360**, 1903–1913 (2002).
29. Dahlof, B. *et al.* Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet.* **366**, 895–906 (2005).
30. Julius, S. *et al.* Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet.* **363**, 2022–20231 (2004).
31. Chung, M., Reitberg, D.P., Gaffney, M. & Singleton, W. Clinical pharmacokinetics of nifedipine gastrointestinal therapeutic system. A controlled-release formulation of nifedipine. *Am. J. Med.* **83**, 10–14 (1987).

32. Verma, R.K., Krishna, D.M. & Garg, S. Formulation aspects in the development of osmotically controlled oral drug delivery systems. *J. Control. Release.* **79**, 7–27 (2002).
33. Kleinbloesem, C.H., van Harten, J., de Leede, L.G., van Brummelen, P. & Breimer, D.D. Nifedipine kinetics and dynamics during rectal infusion to steady state with an osmotic system. *Clin. Pharmacol. Ther.* **36**, 396–401 (1984).
34. Boily, M., Dussault, C., Massicotte, J., Guibord, P. & Lefebvre, M. The impact of new partial AUC parameters for evaluating the bioequivalence of prolonged-release formulations. *Eur. J. Pharm. Sci.* **66**, 70–77 (2015).
35. Yu, L.X. & Li, B.V. 7.4.3 Formulations with Different Release Mechanisms. In: *FDA bioequivalence standards.* eBook ed. 180–181 (AAPS Press: Springer, New York, 2014).
36. Hauck, W.W., Hyslop, T., Chen, M.L., Patnaik, R. & Williams, R.L. Subject-by-formulation interaction in bioequivalence: conceptual and statistical issues. FDA Population/Individual Bioequivalence Working Group. Food and Drug Administration. *Pharm. Res.* **17**, 375–380 (2000).
37. Hermida, R.C., Ayala, D.E., Mojon, A. & Fernandez, J.R. Influence of time of day of blood pressure-lowering treatment on cardiovascular risk in hypertensive patients with type 2 diabetes. *Diabetes Care.* **34**, 1270–1276 (2011).
38. Ohkubo, T. *et al.* Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama study. *J. Hypertens.* **20**, 2183–2189 (2002).

Supplementary information accompanies this paper on the *Clinical and Translational Science* website. (http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1752-8062)