



**EUROPEAN
CARDIOVASCULAR
DISEASE 2007**

Issue 1

EXTRACT

The Unique Adalat Story –
Nifedipine Gastrointestinal
Therapeutic System

a report by

Peter A Meredith

Department of Medicine and Therapeutics,
University of Glasgow, Thee Western Infirmary,
Glasgow

The Unique Adalat Story – Nifedipine Gastrointestinal Therapeutic System

a report by

Peter A Meredith

Department of Medicine and Therapeutics, University of Glasgow, The Western Infirmary, Glasgow

Abstract

Limited financial resources influence medication prescription habits. When substituting a reference drug with an approved generic drug for cost reasons – and there is no other reason for such a substitution – regulatory authorities must ensure bioequivalence between the generic product and the reference formulation. Thus, it is imperative that bioequivalence and interchangeability of generic nifedipine modified-release (MR) formulations available on the market are demonstrated when compared with the reference nifedipine gastrointestinal therapeutic system (GITS). By applying regulatory guidelines, the only MR formulations that should be licensed are those that have been proven to be interchangeable on account of bioavailability or clinical comparisons. Such an approach would lead to unequivocal acceptance by physicians and pharmacists in their desire to avoid untoward clinical effects when switching from one nifedipine MR formulation to another. However, if the regulatory guidelines are not strictly enforced, substitution can potentially lead to an increased risk to patient safety.

Introduction

At a time of resource constraints in the healthcare system worldwide, cost issues increasingly influence medication-prescribing habits. For this reason, healthcare providers encourage physicians and pharmacists to use generic drugs, which offer the single advantage of being cheaper than the original proprietary product. Whether this approach is eventually justified with regard to the efficient and safe treatment of the medical conditions of the patients is often a matter of debate, and definitive clinical studies are usually lacking. Increased awareness of potential adverse clinical consequences of generic therapeutic substitution is warranted.

Physicians and pharmacists alike should be alerted to the critical issues of pharmacokinetic bioequivalence, pharmacokinetic/pharmacodynamic correlations and international guideline recommendations concerning differences between different formulations and, in particular, the various formulations of MR nifedipine.

Nifedipine GITS Formulation

The nifedipine GITS formulation provides a once-daily dosing regimen with a continuous and slow release of the drug into the intestinal tract, resulting in a smooth plasma concentration/time profile. This formulation consists of a two-layer core of nifedipine and osmotic polymer surrounded by a semi-permeable membrane, which contains a precisely laser-drilled hole. When the tablet is ingested, water is absorbed from the gastrointestinal tract through the semi-permeable membrane and the nifedipine-containing core forms a suspension that is released through the laser-drilled hole at a constant rate owing to expansion of the polymer core layer.¹ The GITS formulation delivers nifedipine at a constant rate for approximately 18–22 hours. Pharmacokinetic studies comparing the GITS formulation with immediate-release (capsule) and less sophisticated MR formulation (retard tablet for twice-daily administration) have confirmed the controlled release of nifedipine from the GITS tablet into the intestinal tract, resulting in a smooth, predictable plasma concentration.^{2,3}

Pharmacokinetics and Pharmacodynamics of Different Nifedipine Formulations in Patients with Hypertension

The response to many antihypertensive drugs in an individual patient is determined by the drug disposition (pharmacokinetics) and the relationship between concentration and effect. This is certainly true for the dihydropyridine calcium channel blockers (CCBs) and nifedipine in particular, with the pharmacokinetic characteristics of the specific formulation being the major determinant of the pharmacological response elicited. This is because the rate of delivery of nifedipine into the systemic circulation is an additional factor influencing the antihypertensive response. This has been demonstrated when comparing two regimens of intravenous nifedipine infusions (slow infusion versus bolus/exponential infusion)⁴ or comparing intravenous infusion with immediate-release and an MR tablet.^{3,5} These studies showed that slowly increasing plasma concentrations of nifedipine resulted in heart rate being essentially unchanged while decreasing diastolic and systolic blood pressure (BP) in healthy subjects, as well as in patients with hypertension. In contrast, a rapid increase of nifedipine concentrations resulted in a corresponding increase in heart rate and had no relevant influence on diastolic BP. It was therefore recognised that a predictable and controlled release of nifedipine into the intestinal tract results in a smooth plasma concentration/time profile. This not only has the desired blood pressure-lowering effect, but also avoids an increase in heart rate.

When compared with other formulations of nifedipine, the unique dissolution characteristics of nifedipine GITS translate into distinctly different pharmacokinetic (see *Figure 1*) and haemodynamic profiles in hypertensive patients (see *Figure 2* and *Figure 3*).³



Peter A Meredith is Reader in Clinical Pharmacology in the Department of Medicine and Therapeutics at the University of Glasgow. He has held this appointment since 1997, having previously been a Lecturer and Senior Lecturer in the Department of Materia Medica of the same university. He is based in the Gardiner Institute of the Western Infirmary, Glasgow, where most of his teaching commitments and research are undertaken. His principal research interests are in hypertension and various aspects of clinical cardiovascular pharmacology. His publication list includes over 290 peer-reviewed papers in leading international journals, predominantly in hypertension and clinical pharmacology.

Figure 1 shows that oral dosing with the capsule formulation of nifedipine results in large peak concentrations of the drug being rapidly achieved with subsequent rapid elimination of the drug. The retard formulation (slow-release for twice-daily administration) reduces the peak concentration and delays drug elimination, but only to a limited extent. In contrast, the GITS formulation produces a gradual increase in plasma concentrations of nifedipine, which are then sustained at an almost constant level for at least 24 hours. These distinct pharmacokinetic differences are translated into clinically relevant pharmacodynamic differences (see Figure 2 and Figure 3).

Nifedipine capsules produce modest and short-term reductions in BP accompanied by marked increases in heart rate. In contrast, the nifedipine GITS formulation had little or no effect on heart rate, but had a slow and sustained effect on BP. These highly desirable characteristics were also apparent during maintenance therapy with nifedipine GITS.

Pharmacokinetics of Modified-release Nifedipine Formulations – Are They All The Same?

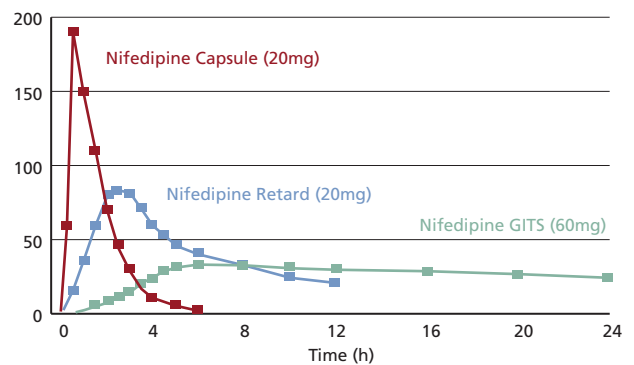
Underlying physiological processes that determine the effect of the dosage form on drug absorption include¹ transit through the gastrointestinal tract;² disintegration of the dosage form;³ dissolution of the active compound;⁴ and absorption from the gastrointestinal lumen into the blood.

The profile of absorption, and thus bioavailability, is controlled by two rate-determining factors: the release of the drug substance from the solid dosage form into solution, and the transport of the drug from the gastrointestinal lumen into the portal vein. Thus, if absorption of the drug substance is rapid and complete, the concentration profile of drug in plasma will be determined by the release of drug from the dosage form. Conversely, if drug absorption is slow, and is therefore the rate-limiting step, the bioavailability is relatively independent of the release of drug from the drug formulation. Clearly, the development of an MR product with the latter characteristic would be expected to be problematic. In contrast, in the former case a highly soluble drug would theoretically lend itself to formulation in an MR preparation.

Nifedipine is not a highly water-soluble drug and thus the development of an MR formulation presented a challenge, particularly the development of a ‘once-daily’ product. The GITS formulation overcame these problems such that delivery of the dosage form is relatively constant over a 24-hour dosing interval. This formulation has been characterised both *in vitro* with dissolution testing and *in vivo* with respect to the plasma concentration time curves. The dissolution profiles show that nifedipine release from the GITS formulation is independent of pH and agitation, both of which can have important effects on the *in vivo* behaviour of the drug formulation within the gastrointestinal tract. It is therefore not surprising that the pharmacokinetic profiles of nifedipine do not differ markedly when the GITS formulation is administered under fasted or fed condition. The absence of a food effect was not shared by all alternative generic once-daily nifedipine formulations and became apparent in case reports on therapeutic problems encountered when switching from the nifedipine GITS to generic nifedipine formulation.⁶

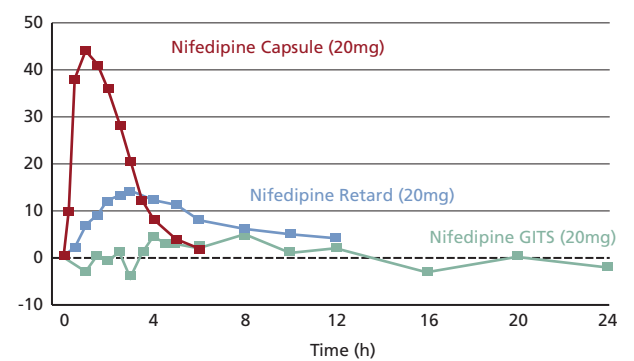
Bioequivalence studies were conducted with several different ‘once-daily’ nifedipine formulations that have been subject to assessment and

Figure 1: Nifedipine Concentration – Time Profiles in Hypertensives: Effect of Formulation



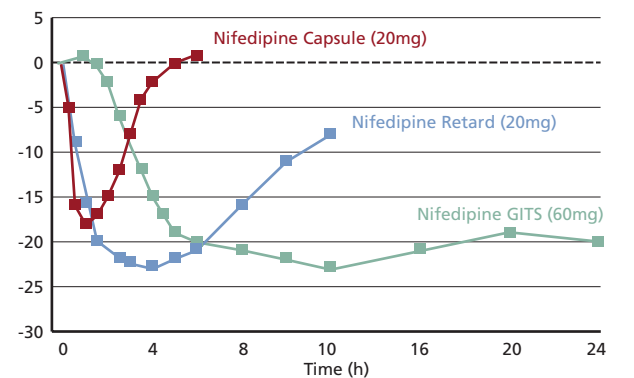
Meredith & Elliott 2004.

Figure 2: Effect of Formulation of Nifedipine on Heart Rate Responses: Placebo-corrected



Meredith & Elliott 2004.

Figure 3: Pharmacokinetic Profiles with Different Once-daily Nifedipine Formulations

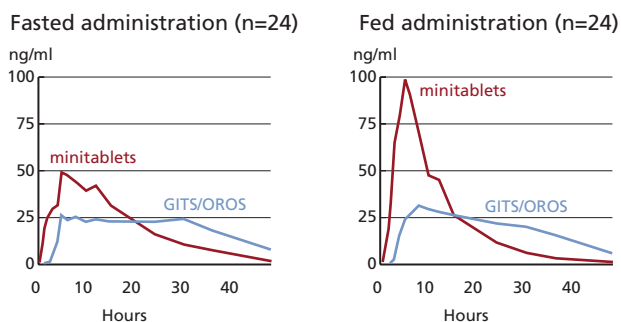


Meredith & Elliott 2004.

have been licensed by the regulatory authorities in the EU.^{7,8} The implication of such approval is that the products are interchangeable and are marketed on the basis that they ‘mimic’ the pharmacokinetic characteristics of nifedipine GITS. Despite this, many fail to do so, particularly in the fed state where there is some evidence of ‘dose dumping’. An example of these discrepancies with an alternative formulation is shown in Figure 4.⁷

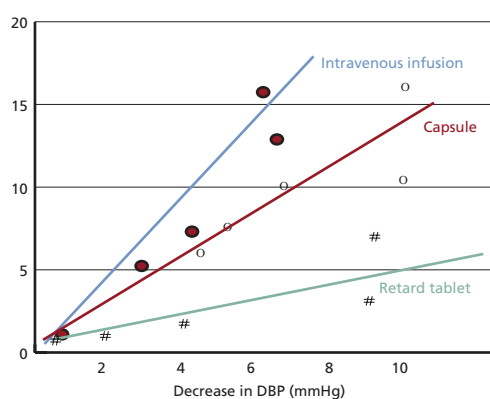
It should be noted that these representations are mean nifedipine

Figure 4: Nifedipine Once-daily Generic



Schug et al., Eur J Pharm Sci, 2002.

Figure 5: Formulation-Dependent Activation of the Sympathetic Nervous System



Kleinbloesem et al., Clin Pharm Ther, 1984;35(6):742-9.

plasma concentration profiles. Analyses of the individual profiles showed there was much greater variability between the alternative formulations and nifedipine GITS, particularly when the drugs were administered after a meal.

Nifedipine once-daily products may not differ markedly in single-dose studies with fasted administration. However, after fed administration, none of the generics tested were bioequivalent to nifedipine GITS.⁷ This has important implications for therapy as the products are not interchangeable and there must be some safety concerns regarding the 'dose dumping' effect, i.e. the premature release of the drug, observed in some cases.⁹

Clinical Effects of Nifedipine Plasma Concentrations

Chronic activation of the sympathetic nervous system (SNS) may lead to hypertension, tachycardia, regional ischaemia, atherosclerosis and thrombosis. Changes in the SNS are apparent when a pressor agent is administered, with increases in BP and reduced heart rate and sympathetic activity, as shown by reductions in levels of plasma noradrenaline. Conversely, vasodilators decrease BP and increase sympathetic activity, as shown by increases in both heart rate and plasma levels of noradrenaline. The rate at which BP is lowered determines the sympathetic activation response. Rapid BP reductions with vasodilators produce almost immediate increases in heart rate and levels of circulating catecholamines. This observation is also apparent with different formulations of the same drug. Thus, intravenous infusions of nifedipine

(see Figure 5) produce a rapid reduction in BP and marked reflex tachycardia.⁵ Compared with intravenous administration, the capsule formulation of nifedipine diminishes the rate at which BP is lowered, thereby decreasing the heart rate response slightly; the retard formulation (slow-release formulation for twice-daily administration) reduces the reflex response even further.

These phenomena are rarely apparent in routine practice as BP is rarely assessed at the time of peak drug concentrations, or in most clinical trials where the focus tends to be on effects at trough at the end of the dosing interval. However, important differences between drug formulations are apparent in investigations that have focused on effects at the time of peak plasma drug concentrations.¹⁰ In such a study, a once-daily MR formulation of nifedipine was compared with nifedipine GITS in a cross-over design with treatment being switched after two weeks. Peak nifedipine plasma concentrations were achieved at four hours after the first dose of the generic MR formulation and at six hours after nifedipine GITS. Systolic BP decreased rapidly after the first dose of the generic MR formulation, achieving a nadir at five hours post-dose, accompanied by a slight rise in heart rate. After nifedipine GITS, heart rate fell slightly. At the time of peak drug concentration, plasma noradrenaline was higher in patients receiving the generic MR formulation than those receiving nifedipine GITS and the change from baseline was statistically significantly different. A similar difference between the drugs was seen again at days 15 and 29, at five hours after switching formulations. After two weeks of treatment the noradrenaline pattern persisted, but was less marked. Switching between formulations caused opposite effects upon the sympathetic nervous response to falling BP. These acute differences are unlikely to be apparent on single time-point clinic visits, but may lead to clinically important differences in risk for patients.

Comparisons of nifedipine retard (slow-release formulation for twice-daily administration) and nifedipine GITS demonstrate that, both in first dosing and at steady state, the fluctuating plasma drug concentrations with the MR formulation result in fluctuating BP control and dose-related increases in heart rate.¹¹ In contrast, changes in BP and heart rate are smooth and consistent with nifedipine GITS over the dosage interval, both acutely and at steady state. With nifedipine retard (slow-release formulation for twice-daily administration), plasma levels of noradrenaline are significantly increased both on first dosing and at steady state two to four hours post-dose. However, there is no evidence of activation of the SNS with the GITS formulation of nifedipine.

These findings are supported by a systematic review of the published literature.¹² With acute administration, the immediate-release formulations of nifedipine and felodipine reduce BP, produce reflex tachycardia and increase plasma noradrenaline levels. The same effects are seen for maintenance therapy with, if anything, greater reductions in BP and greater increases in plasma noradrenaline. Studies at steady state using the MR formulations of the two drugs produced disparate findings. With nifedipine GITS, the 25% average reduction in mean arterial pressure did not promote any reflex activation, as shown by the absence of heart rate or plasma noradrenaline responses. In contrast, with felodipine extended-release formulation, the BP reduction was more modest but reflex activation was apparent with increases in both heart rate and plasma noradrenaline.¹³

The evidence indicates that, for dihydropyridine CCB, plasma drug levels are closely linked to BP reduction. The rate at which plasma concentration (t_{max}) increases is important, but this parameter is often poorly defined and is not considered as primary in bioequivalence studies. The pharmacokinetics of different once-daily nifedipine formulations are not the same, and thus it is highly unlikely that they have directly similar pharmacodynamic properties. Different formulations of the same dihydropyridine CCB can have negative effects by stimulating the SNS, thereby increasing the potential for adverse events.

In conclusion, all once-daily nifedipine formulations are not pharmacokinetically, and likely not pharmacodynamically, the same. Short-acting formulations are associated with sympathetic activation triggered by a more abrupt fall in BP. Thus, considerable caution must be exercised and interchangeability of different formulations cannot be assumed even if clinical or trough BP control seems to be similar.

Regulatory Aspects – Bioequivalence Criteria in Europe and North America

There is no other rationale for generic drug substitution other than cost savings and thus regulatory authorities must require adequate parameters to ascertain bioequivalence between the generic product and the reference formulation.

Guidelines

The assessment of bioequivalence for MR oral dosage forms in Europe is based upon regulatory guidance.^{14,15} In the US and Canada, the guidelines specifically state that “drug products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling”.¹⁶

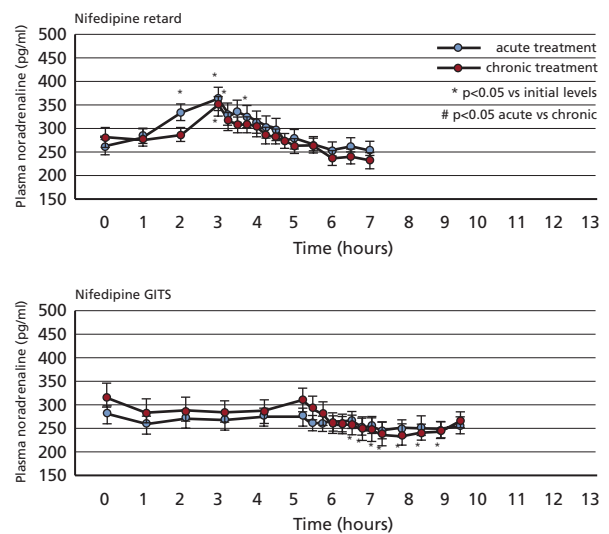
For bioequivalence to be established, the rate and extent of absorption of the test drug should not differ significantly from the rate and extent of absorption of the reference drug when administered at the same molar dose of the therapeutic ingredient, under similar experimental conditions and as either a single dose or multiple doses. To demonstrate this, the study should have a power of 80% to detect a difference of at least ±20%. In addition, the 90% confidence interval of the mean relative area under the plasma concentration versus time curve (AUC) and maximum plasma concentration (C_{max}) values must be in the 80–125% range. In North America, for drugs with a narrow therapeutic index, 95% confidence intervals are used instead, whereas European guidelines ask to tighten the acceptance interval without specifying it.¹⁵ It is also stated that statistical evaluation of time to maximum plasma concentrations (t_{max}) makes sense only if there is a clinically relevant claim for rapid release, rapid onset of action or signs related to adverse effects.¹⁵

Evaluation of reference formulations should be performed under single-dose and steady-state conditions, including the influence of a food effect on the pharmacokinetics after single-dose administration of both formulations.¹⁴

Pharmaceutical Equivalence versus Bioequivalence

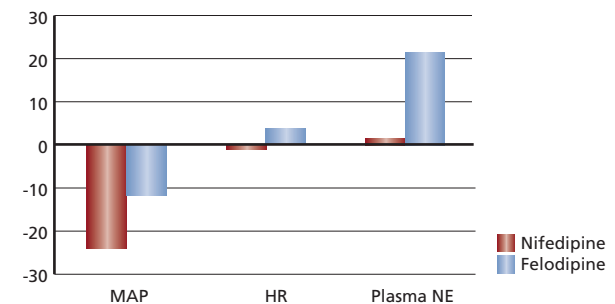
Pharmaceutical equivalence does not necessarily imply bioequivalence, since excipients or the manufacturing process can lead to faster or slower dissolution or absorption. *In vitro* dissolution data at different

Figure 6: Nifedipine – Effect of Formulation on Reflex Activation – Profiles of Plasma Noradrenaline with Time



de Champlain et al., J Hypertension, 1998;16:1357-69.

Figure 7: Studies Reporting the Long-term Effects of Long-acting Dihydropyridines



Grossman and Meserli, AMJ Cardiol, 1997;80:1453-8.

pH values may indicate distinct differences between the test and reference formulations. Nifedipine GITS showed identical mean dissolution profiles at different pH values, whereas test formulations may show relevant differences, leading to potential changes in pharmacokinetics *in vivo*.

It is of utmost importance that the specifications for the *in vitro* dissolution of the test product should be derived from the dissolution profile of the batch that was found to be bioequivalent to the reference product and would be expected to be similar to those of the reference product. Changes in production site may contribute to relevant differences regarding *in vitro* dissolution tests. Usually, a change in the manufacturing site does not require data from an additional bioequivalence study but only from *in vitro* dissolution tests. These tests are to be performed with the assay method used for quality control for release of production batches. However, *in vitro* and *in vivo* correlation is not requested for the time being. There is further potential for confusion for the prescriber in that some generic nifedipine MR formulations were approved on the basis of pharmacokinetic similarity, others on the basis of pharmacodynamic similarity, i.e. BP-lowering effects. Transparency regarding such

information is warranted. However, regulatory authorities may not provide such transparency on particular approvals because of confidentiality reasons. In some countries, though, 'freedom of information' makes such data accessible.

Interchangeability of 'Bioequivalent' Drugs

Despite using similar approaches for generic drug regulation, the US and Canada have quite discrepant views regarding the interchangeability of 'bioequivalent' drugs.

In the US, the attitude is determined by the view that "to date, there are no documented examples of a generic product manufactured to meet its approved specifications that could not be used interchangeably with the corresponding brand-name drug".¹⁷ Furthermore, a US Food and Drug Administration (FDA) official has stated that "if one therapeutically equivalent drug is substituted for another, the physician, pharmacist and patient have the FDA's assurance that the physician should see the same clinical results and safety profile".¹⁸ This principle has been applied universally in the US and it is not necessary for the healthcare provider to approach any one therapeutic class of drug products differently when the FDA has determined that they are equivalent. This principle is considered true even if a product has a narrow therapeutic index.¹⁹ Not only does the FDA-approved product labelling suggest that additional tests need not be performed by the healthcare provider when switching from a brand-name drug product to a generic equivalent, but also that the same applies when switching from a generic equivalent to an alternative generic product when both are deemed equivalent to the brand-name drug product.

In contrast, although the Health Canada Therapeutic Products Directorate is responsible for the review of bioequivalence and has responsibility for the issue of a Notice of Compliance (NOC) that assures that the generic is safe, effective and equivalent to a standard reference product, it will not declare that these products are interchangeable. Thus, the onus rests with the prescriber or pharmacist to make the decision as to whether the patients will obtain equivalent clinical benefit by switching to the alternative dose form.

Although some small differences exist between the US and Canada in assessing the bioequivalence of generic drugs, the differences are fundamental in the way that the two countries interpret the data. The FDA considers their regulations and procedures as sufficiently stringent to guarantee that generic products should provide the same clinical efficacy and safety as the innovator product. However, in Canada, the federal regulatory authorities do not declare that products are interchangeable and the burden of responsibility rests with the Canadian provinces; however, it is the physician and pharmacist who ultimately control generic substitution, which is at their own risk.

Several countries, including the UK and South Africa, permit non-equivalent generic MR nifedipine formulations to be prescribed and dispensed; however, they acknowledge that these medicines are likely different and should not be interchanged. As stated in the British National Formulary 52, "different versions of MR preparations may not have the same clinical effect. To avoid confusion between these different formulations of nifedipine, prescribers should specify the brand to be dispensed".²⁰

Clinical Implications and Patient Outcome

To arrive at qualified therapeutic decisions, the prescribing physician should have reasonable expectations of a high-quality MR BP-lowering agent, in particular with regard to nifedipine. The physician should be made aware of the determination of bioequivalence and the potential clinical implications of interchangeability or substitution between the various MR formulations of nifedipine. The physician's primary objective must remain the appropriate and safe management of the patient's condition.

In this context, the questions are whether nifedipine GITS is really 'unique', and, if so, does the 'uniqueness' really matter? Nifedipine GITS is uniquely able to provide gastrointestinal release of nifedipine at a constant rate that approximates to a steady intravenous infusion (the near 'zero-order infusion process' without the inconvenience of intravenous administration). GITS is the only MR preparation of nifedipine that has undergone two large-scale, double-blind, randomised trials in hypertension and angina and to have demonstrated unequivocal benefits in both studies.^{21,22} No other MR preparation of nifedipine has demonstrated evidence of comparable efficacy to nifedipine GITS in clinical outcome studies or definitive evidence of bioequivalence to nifedipine GITS. In the latter case, differences in C_{max} , AUC and t_{max} that have been quantified in published studies⁷⁻⁹ are clinically important and therefore do matter in clinical practice. Such clinical implications for patient care include:

- tachycardia with the possibility of faintness and palpitations associated with the rapid rise and higher plasma concentrations of nifedipine early in the dosing interval;
- lack of 24-hour BP control; and
- unnecessary addition of other medications in case of lower plasma concentrations later in the dosing interval.

Rate and extent of fluctuations of plasma concentrations are clinically important for the CCB nifedipine. Large fluctuations cause swings in BP, potentially serious hypotension with complications and activation of the SNS. Differences in nifedipine MR formulations are clinically important. Other nifedipine MR preparations do not demonstrate the same constant plasma concentrations and smooth BP-lowering effects as nifedipine GITS. Regulatory authorities should be encouraged to license only MR nifedipine formulations that are interchangeable on account of bioavailability or clinical comparisons. It is imperative that physicians are made aware of the potentially untoward clinical implications of inferior nifedipine MR preparations as substitutes for the nifedipine GITS product.

Conclusions

Limited financial resources continue to influence medication prescription habits. When substituting a reference drug with an approved generic drug for cost reasons, regulatory authorities should ensure bioequivalence between the generic product and the reference formulation. The current generic nifedipine MR formulations available on the market do not possess conclusive evidence of bioequivalence and interchangeability. By applying regulatory guidelines, only MR formulations that have been proven to be interchangeable on account of bioavailability should be licensed. Such an approach would lead to unequivocal acceptance by physicians and pharmacists to avoid unnecessary potential safety risks to the patient that may result when switching from one nifedipine MR formulation to another. ■

1. Swanson DR, Barclay BL, Wong PS, Theeuwes F, Nifedipine gastrointestinal therapeutic system, *Am J Med*, 1987 Dec 21;83(6B):3–9.
2. Toal CB, Formulation dependent pharmacokinetics-does the dosage form matter for nifedipine?, *J Cardiovasc Pharmacol*, 2004 Jul;44(1):82–6.
3. Meredith PA, Elliott HL, Dihydropyridine calcium channel blockers: basic pharmacological similarities but fundamental therapeutic differences, *J Hypertens*, 2004 Sep;22(9):1641–8.
4. Kleinbloesem CH, van Brummelen P, Danhof M, et al., Rate of increase in the plasma concentration of nifedipine as a major determinant of its hemodynamic effects in humans, *Clin Pharmacol Ther*, 1987 Jan;41(1):26–30.
5. Kleinbloesem CH, van Brummelen P, van de Linde JA, et al., Nifedipine: kinetics and dynamics in healthy subjects, *Clin Pharmacol Ther*, 1984 Jun;35(6):742–9.
6. Rayner B, Buchanan-Lee B, Brink J, Opie L, Generic substitution—is it safe in patients at high cardiovascular risk?, *S Afr Med J*, 2002 Aug;92(8):603–4.
7. Schug BS, Brendel E, Wolf D, et al., Formulation-dependent food effects demonstrated for nifedipine modified-release preparations marketed in the European Union, *Eur J Pharm Sci*, 2002 Apr;15(3):279–85.
8. Schug BS, Brendel E, Wonnemann M, et al., Dosage form-related food interaction observed in a marketed once-daily nifedipine formulation after a high-fat American breakfast, *Eur J Clin Pharmacol*, 2002 May;58(2):119–25.
9. Wonnemann M, Schug B, Schmucker K, et al., Significant food interactions observed with a nifedipine modified-release formulation marketed in the European Union, *Int J Clin Pharmacol Ther*, 2006 Jan;44(1):38–48.
10. Brown M, Watts M, Mackenzie J, et al., Formulation of long acting nifedipine tablets influences the heart rate and sympathetic nervous response in hypertensive patients, *J Hypertens*, 2005;23 (suppl 2):S306 (abstract).
11. de Champlain J, Karas M, Nguyen P, et al., Different effects of nifedipine and amlodipine on circulating catecholamine levels in essential hypertensive patients, *J Hypertens*, 1998 Sep;16(9):1357–69.
12. Croom KF, Wellington K, Modified-release nifedipine: a review of the use of modified-release formulations in the treatment of hypertension and angina pectoris, *Drugs*, 2006;66(4):497–528.
13. Grossman E, Messerli FH, Effect of calcium antagonists on plasma norepinephrine levels, heart rate, and blood pressure, *Am J Cardiol*, 1997 Dec 1;80(11):1453–8.
14. Committee for Proprietary Medicinal Products (CPMP), Note for guidance on modified release oral and transdermal dosage forms, Section II (pharmacokinetic and clinical evaluation), CPMP/EWP/280/96: European Agency for the Evaluation of Medicinal Products (EMA); 1999.
15. Committee for Proprietary Medicinal Products (CPMP), Note for guidance on investigation of bioavailability and bioequivalence, CPMP/EWP/QWP/1401/98: European Agency for the Evaluation of Medicinal Products (EMA); 2001.
16. FDA Center for Drug Evaluation and Research (CDER), Orange Book – Approved drug products with therapeutic equivalence evaluations, 26th ed, 2006.
17. Nightingale SL, Associate Commissioner for Health Affairs, FDA Center for Drug Evaluation and Research (CDER), Therapeutic equivalence of generic drugs, Letter to health practitioners, 1998.
18. Williams RL, Deputy Center Director for Pharmaceutical Science; FDA Center for Drug Evaluation and Research (CDER), Therapeutic equivalence of generic drugs, Response to National Association of Boards of Pharmacy, 1997.
19. FDA comments on activities in states concerning narrow-therapeutic-index drugs, *Am J Health Syst Pharm*, 1998 Apr 1;55(7):686–7.
20. British National Formulary 52. Modified release formulations of nifedipine, 2006; available at http://bnf.org/bnf/bnf/current/2693.htm?q=%22different%20of%20of%20nifedipine%22#_hit
21. Brown MJ, Palmer CR, Castaigne A, 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*, 2000 Jul 29;356(9227):366–72.
22. Poole-Wilson PA, Lubsen J, Kirwan B-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*, 2004;364:849–57.

WWW.TOUCHBRIEFINGS.COM



Cardinal Tower
12 Farringdon Road
London
EC1M 3NN

EDITORIAL Tel: +44 (0) 20 7452 5181
Fax: +44 (0) 20 7452 5050

SALES Tel: +44 (0) 20 7452 5164
Fax: +44 (0) 20 7452 5606

E-mail: info@touchbriefings.com
www.touchbriefings.com