Integrated Blood Pressure Control

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REVIEW

A review of the gastrointestinal therapeutic system (GITS) formulation and its effectiveness in the delivery of antihypertensive drug treatment (focus on nifedipine GITS)

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Abstract: Hypertension treatment guidelines do not discriminate within drug classes and, furthermore, do not consider whether or not all of the formulations of any given drug licensed for once-daily administration can be considered to be therapeutically interchangeable. This article focuses on this issue with respect to nifedipine and the development of the gastrointestinal therapeutic system (GITS) formulation. Nifedipine GITS is regarded as the gold standard once-daily formulation of nifedipine and, as such, it is anticipated that alternative formulations will be therapeutically equivalent to nifedipine GITS. In general, this depends on demonstrating pharmacokinetic bioequivalence. This article is intended to focus attention on generic substitution and, in particular, on aspects of the scientific basis for the substitution of generic products in place of branded products. Such substitution is required for cost-saving or cost-containment reasons and is justified on the basis that the generic (substitute) drug is "therapeutically" equivalent to the branded drug. Unfortunately, there are serious shortcomings in the current methods of assessment insofar as they are typically based on statistical comparisons of average pharmacokinetic parameter values, using arbitrary comparative criteria. This article illustrates the shortcomings of the current approaches to generic substitution and concludes that, in regulatory terms, either more rigorous pharmacokinetic criteria are required or pharmacodynamic indices should be added to reinforce the regulatory criteria. Generic substitution is a balancing act but, at the moment, the cost issue is dominant. To restore the balance, equivalent efficacy must be confirmed. At present, therefore, in the absence of such regulatory rigor, the obvious course is to prefer the branded product, the therapeutic efficacy of which (including outcome benefits) has been established.

Keywords: nifedipine GITS, generic, generic substitution, bioequivalence, cardiovascular outcome, safety

Introduction

While lifestyle modifications are an integral part of the treatment of hypertension, all the major hypertension treatment guidelines agree that the benefits in terms of reduced cardiovascular morbidity and mortality are associated with improved blood pressure control by means of antihypertensive drug treatment.[1–4] There is some disagreement, however, with respect to the selection of drugs for initiating therapy.

The guidelines from USA (The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [JNC 7]) suggest that a thiazide-type diuretic is most suitable for initiating treatment in stage I

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hypertension and is the drug of choice as a combination partner with alternative types of antihypertensive drug for the treatment of stage II hypertension.[1] In contrast, the European guidelines[2] suggest that all five major classes of antihypertensive agent are suitable for the initiation and maintenance of antihypertensive treatment, either alone or in combination. However, while the European guidelines consider that all drugs are "equal" as monotherapy, there is clear discrimination with respect to those drug combinations that are to be preferred, and it is noteworthy that calcium channel blockers are the only class of agent deemed desirable for combination with all the other four classes of antihypertensive drug.[2]

Irrespective of the drug class, and albeit with some exceptions,[4] there is general acceptance within these guidelines that the outcome benefits of each different type of antihypertensive drug treatment can be considered to be a "class" effect. The shortcomings of this presumption of a class effect are well illustrated by considering angiotensin-converting-enzyme inhibitor drugs (ACEIs) and the outcome evidence with individual agents. In the 1990s, and on the assumption of a class effect, ten ACEIs were licensed for the treatment of hypertension in the USA: five had no outcome data, three relied on trials using surrogate end points and, therefore, only two of the ten had outcome evidence in hypertension.[5]

The presumption of a class effect becomes even more problematic when considering calcium channel blocking drugs (CCBs). There are the well-recognized clinical pharmacological differences between the "rate-limiting" agents, verapamil and diltiazem, and the dihydropyridine group of CCBs; less well-recognized and often ignored are the significant differences between agents within the dihydropyridine group and between different formulations of the same dihydropyridine. These differences translate to distinct differences in the therapeutic profiles and are likely to translate into differences in outcome during long-term treatment. Since there are significant differences in the pharmacokinetic, pharmacodynamic, and therapeutic profiles, caution should be exercised in assuming that all dihydropyridine CCBs are equivalent in terms of their durations of action and overall antihypertensive efficacy.[6] Furthermore, in practical terms, one of the main issues is whether or not all of the formulations (of any given dihydropyridine drug) licensed for once-daily administration can be considered to be therapeutically interchangeable. This is the focus of this review with respect to nifedipine and the development of the gastrointestinal therapeutic system (GITS) formulation.

Nifedipine

Historical perspective

Nifedipine is the prototype dihydropyridine CCB, first introduced in the mid-1970s, initially for the prevention of angina symptoms and later for the treatment of hypertension.[7] The primary pharmacodynamic effect of nifedipine is dilatation of both large and small arteries through a reduction in smooth muscle contraction in the arterial wall.[7] Nifedipine has little net effect on cardiac contractility or conduction and, in addition to its vasodilatory actions, it also demonstrates antiatherosclerotic activity.[7]

The administration of the original formulation of nifedipine (immediate-release capsules) was associated with profound reflex increases in heart rate and activation of the sympathetic nervous system.[7] Since it was recognized that the rate of delivery of nifedipine into the systemic circulation was a direct determinant of the rate of onset of the vasodilator effect and, in turn, of the extent of the reflex sympathetic activation, alternative, modified-release formulations were then developed.

The retard formulation of nifedipine blunted the peak concentration and sustained the measurable drug levels over a longer period.[8] Consequently, there was a more sustained reduction in blood pressure, allowing twice-daily administration, but, although more modest, there was still a significant increase in heart rate.[9] The development of the GITS formulation finally resulted in a formulation that delayed and flattened the attainment of the peak plasma concentrations of nifedipine and thereafter sustained these levels at a relatively constant level for 24 hours. This results in a smoother, more gradual onset of the antihypertensive effect, sustained throughout 24 hours with no discernible cardioacceleration.[7,10]

The efficacy of monotherapy or combination therapy with nifedipine GITS has been established in numerous studies in hypertension and angina, and these have been extensively reviewed elsewhere.[7] Nifedipine GITS is approved for the treatment of hypertension and the prophylaxis of angina pectoris in a large number of countries worldwide. Furthermore, it is the GITS formulation of nifedipine that was used in the major outcome trials, INSIGHT and ACTION. In these trials, nifedipine GITS was effective in significantly reducing the major complications of hypertension[11] and coronary artery disease.[12]

The nifedipine GITS formulation

The once-daily nifedipine GITS formulation is based on osmotic push–pull technology and consists of a bilayer core

of nifedipine and an osmotically active but pharmacologically inert polymer surrounded by a semipermeable membrane.[13] After the tablet enters the gastrointestinal tract, it absorbs water to create a nifedipine suspension in the drug reservoir. Then, as the polymer expands and the osmotic pressure increases, the drug suspension is extruded through the precision-drilled pore at a controlled rate over 24 hours (Figure 1). This unique osmotic delivery system delivers nifedipine into the gastrointestinal system and hence into the systemic circulation at a constant (zero-order) rate until the formulation is exhausted.

Other once-daily formulations

Osmotic controlled delivery systems

The GITS bilayer tablet is only one type of osmotic controlled delivery system, but there also are alternative osmotically controlled drug release oral delivery systems (OROS): monolayer, bilayer, and multilayer systems.[14] The simple monolayer tablet consists of the osmotic core (containing drug) surrounded by a semipermeable membrane and a hole crossing the membrane acting as a drug delivery orifice. Following ingestion, as water crosses the semipermeable membrane, the osmotic polymers expand and the solution of drug is delivered into the gastrointestinal system via the orifice.[15] This process continues until the osmotic pressure inside and outside the tablet is equalized. The advantage of this elementary osmotic pump system is that the release of the drug is largely independent of physiologic factors.[15] However, the rate of drug release is affected by the solubility of the drug, swelling and wetting agents in the core, osmotic pressure, orifice size and shape, and membrane properties.[14–17] The size of the delivery orifice is important in that the maximum size must be smaller than the osmotic expansion polymer but large enough to allow drug in solution to cross, since both are mixed together in the monolayer tablet.

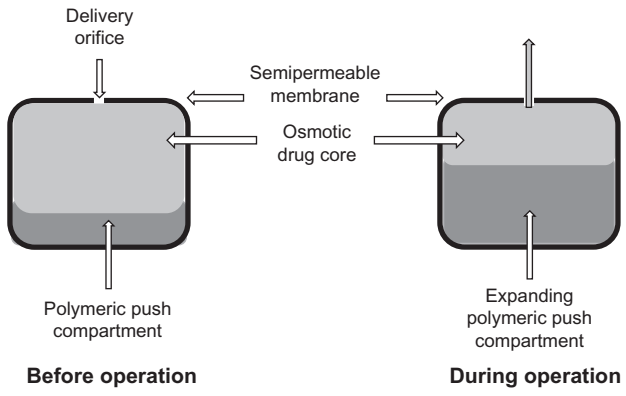

Figure 1 Diagrammatic representation of the gastrointestinal therapeutic system (GITS).

The one common feature of all these OROS systems is that the "tablet" shell does not dissolve but passes through the gastrointestinal system intact and is expelled upon defecation. Transit time through the gastrointestinal system and transport of drug across the gut wall into the blood will thus have an impact on drug bioavailability.[18]

Unlike nifedipine GITS, there is a relative paucity of clinical data with alternative once-daily nifedipine formulations as they have, in general, been licensed on the basis of bioequivalence studies. There are however, some head-to-head comparisons, which will be discussed later.

Alternative delivery systems

A number of other once-daily nifedipine formulations have been manufactured. These have employed erosive tablet technology,[19] a capsule containing several mini tablets,[20] hydrophilic matrix tablets,[21] a monolithic enteric-coated-like tablet with an erosive polymer matrix,[22] an eroding matrix,[23] and a monolayer matrix.[24]

Comparisons of different drugs and formulations

Direct, comparative outcome studies within a drug class are rare and therapeutic equivalence is usually assumed via comparisons of published papers that have separately evaluated the drugs in question. Equivalence is then assumed on the basis of results that are similar, but which cannot be directly compared in statistical terms. There also are issues relating to the fact that these different studies have usually been generated by different research groups, in different patient populations, using slightly different methodologies, etc.

Regulatory requirements

Most once-daily nifedipine formulations have been licensed for clinical use on the basis of establishing "essential similarity" to the reference innovator product (in this case, nifedipine GITS) and this is normally pivotally dependent upon a bioequivalence study.

Although the regulatory requirements for establishing bioequivalence vary from country to country, they are fundamentally similar. Bioequivalence may be defined as:

> the rate and extent of absorption of the test drug do not show a significant difference 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 in either a single dose or multiple doses.[25]

In practice, these characteristics are defined by pharmacokinetic parameters. These include area under the curve (AUC) to the last measurable concentration (AUC_{0-t}), AUC to time infinity ($AUC_{0-\infty}$), and maximum concentration (C_{max}), obtained from the plasma concentration versus time profiles. The time to maximum concentration (t_{max}) is also formally reported but, unlike other parameters, is not subject to formal analysis. In studies to determine bioequivalence, the parameters to be analyzed are AUC and C_{max}. For these parameters, the 90% confidence interval (CI) for the ratio of the test and reference products should be contained within the acceptance interval of 80%–125%.[26] All regulatory authorities require that, for modified-release formulations, bioequivalence is established with single-dose studies in both the fasting and fed states. In addition, some authorities, including in Canada and Europe, demand that bioequivalence is also established after multiple doses at steady state.[26]

Regardless of the small differences in regulatory approaches, it is important to note that all bioequivalence studies are conducted in relatively small groups of normal healthy volunteers (usually less than 40 individuals) based on pharmacokinetic parameters. The grant of market approval does not demand the establishment of therapeutic equivalence or indeed any appropriate comparative clinical studies in the target patient population.

Bioequivalence evaluations

For the majority of modified-release compounds available on the market today, the present regulatory guidelines are deemed to be robust based on a lack of evidence of deleterious effects associated with generic substitution.[27] Indeed, in the past, a US Food and Drug Administration (FDA) official 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."[27] This principle has been applied universally in the US and it is not deemed necessary for the health care provider to approach any single therapeutic class of drug products differently, ie, there are no exceptions once the FDA has determined that products are equivalent. This is considered to be true even if a product has a narrow therapeutic index.[28] Thus, the FDA considers that their regulations and procedures are sufficiently stringent to guarantee that generic products should provide the same clinical efficacy and safety as the innovator product. This will often be true, but, in reality, the only guarantee that can be made is that there are unlikely to be substantial safety issues associated with switching to and between generic products and that "absence of evidence" is not synonymous with "evidence of absence." Such statements should be interpreted with some caution, however, and there is certainly evidence that such caution should be exercised with once-daily nifedipine formulations, as it has become apparent in recent years that many are not interchangeable with nifedipine GITS.

Fed and fasted pharmacokinetics

A series of studies, which are discussed below, have been conducted with non-OROS formulations of nifedipine and a concerning degree of commonality has been observed in these studies. In many instances, significant food interactions were observed, leading to a lack of consistency of drug release from the "copy" formulations (ie, considerable fed/fasted alterations to the drug-release characteristics). These fed/fasted differences could also be detected in in vitro dissolution experiments under differing pH conditions mimicking the expected physiological range in the gastrointestinal tract.

In the first reported comparative study of nifedipine GITS, a hydrophilic matrix tablet of nifedipine based on hydroxypropyl methylcellulose as the gel-forming agent was shown to have a highly significant ($P < 0.001$) increase in AUC and C_{max} with food relative to the fasting state after a single dose.[21] Similar discrepancies have been seen in other comparative studies. For example, dissolution testing in vitro using standard United States Pharmacopeia (USP) methodology showed that an erosive polymer matrix exhibits properties similar to an enteric coated tablet and pH dependent dissolution with drug undetectable at pH 4.8 but comparable to nifedipine GITS at pH 6.8.[22] In contrast, nifedipine GITS was unaffected by pH in the dissolution experiments. Some differences between the formulations were apparent under fasting conditions and these were even more exaggerated after food.[22]

A further study compared an erosive tablet to nifedipine GITS by in vitro dissolution testing and single-dose fasting and fed pharmacokinetic testing in healthy volunteers.[21] In vitro dissolution testing showed nifedipine GITS to provide consistent drug release across all pH values, whereas the erosive tablet formulation exhibited inconsistent and incomplete release. In vivo, after fasted administration, the plasma concentration–time curves were comparable for the two formulations, although formal statistical evaluation of the pharmacokinetic parameters in the fasted state failed to demonstrate bioequivalence with a point estimate for C_{max} of 0.87 (95% CI: 0.74–1.03) and a point estimate for $AUC_{0-\infty}$ of 0.81 (95% CI: 0.67–0.99). However, after food, the plasma

concentration–time profiles were quite disparate. Nifedipine GITS had a profile very similar to that of the fasting state, while the erosive tablet formulation exhibited a sharp rise in concentration within the first 5 hours after administration. Statistical evaluation after food again failed to demonstrate bioequivalence but this time in the opposite direction, with a point estimate for C_{max} of 2.35 (95% CI: 2.00–2.76) (Figure 2).

Several other studies have confirmed these findings with other once-daily nifedipine formulations. Formulations utilizing capsules containing mini tablets,[20] an eroding matrix,[21] and a monolayer matrix[22] all exhibited similar discrepancies when compared to nifedipine GITS. In all cases, this was characterized by inconsistent in vitro release properties at different pH values and a failure to demonstrate pharmacokinetic bioequivalence to nifedipine GITS. This lack of bioequivalence was particularly apparent under fed conditions, with significantly higher C_{max} and AUC values.

Thus, for all the nonosmotic release formulations tested (erosive matrices, erosive polymers, monolayer matrices, erosive technology, or capsules with mini tablets) bioequivalence to the reference formulation nifedipine GITS was not confirmed when the test drug was administered with food. In general, there were significant alterations in the plasma concentration–time relationship in both the extent and the rate of drug absorption for each of the test formulations compared to nifedipine GITS. It is also important to note that, when the concentration–time curves for individual subjects were examined, the non-GITS formulations exhibited considerable inter-subject variability, while, in contrast, there was minimal inter-subject variability in either the fasted or fed studies with the nifedipine GITS.[20,24]

There is a relative paucity of studies comparing different osmotic delivery technologies for nifedipine. In one study in which a monolayer osmotic release system was compared to nifedipine GITS,[29] overall the in vitro dissolution profiles of both formulations showed similar patterns analogous to zero-order release, but the curve for the monolayer osmotic release system exhibited a longer lag time before release of drug and lower overall quantity of release over 24 hours. In vivo evaluation suggested that the mean plasma concentration–time curves differed between the two osmotic formulations under fasting and fed conditions. Under fasting conditions the reference product (nifedipine GITS) showed an earlier onset of drug absorption with plateau achieved at approximately 4 hours whereas the test formulation exhibited a longer lag time and achieved plateau levels after 10 hours. Notably, this longer lag time was observed in all subjects. The plateau phase was observed for almost 20 hours in the reference formulation but for only 14 hours in the test formulation. After food, the plasma concentration–time profiles for each formulation had similar-shaped profiles, but the test formulation exhibited a longer lag time to drug absorption and almost 20% lower overall plasma concentrations over 36 hours of measurement.

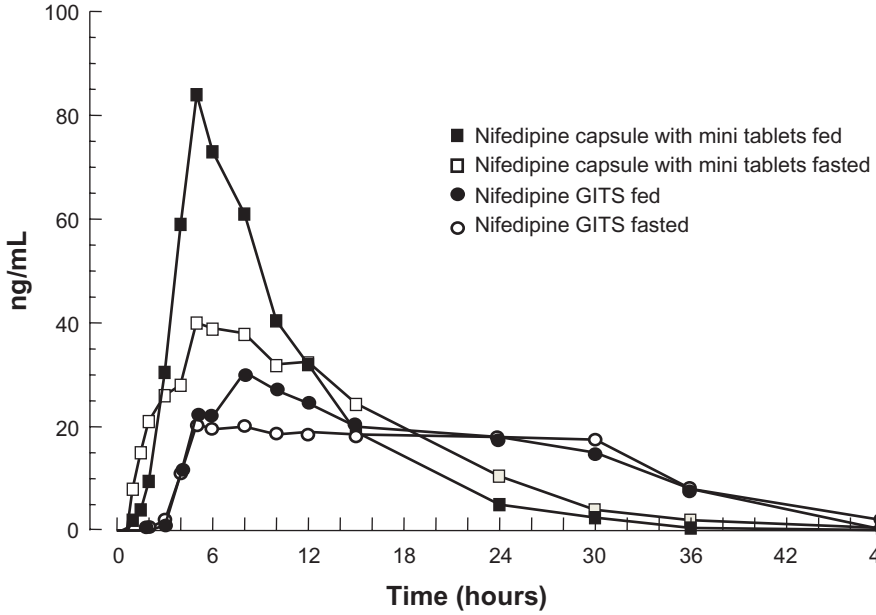

Figure 2 Geometric mean plasma concentration–time curves after single-dose administration of 30 mg nifedipine gastrointestinal therapeutic system (GITS) (reference formulation) and an erosive modified-release formulation of nifedipine (test formulation) in healthy subjects under fed conditions. Copyright © 2002, Springer. Adapted with permission from 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;58(2):119–125.[20]

Statistical evaluation of the pharmacokinetic parameters in the fasted state revealed lower $AUC_{0-\infty}$ values for the monolayer osmotic release system versus nifedipine GITS (point estimate 87.9%, 90% CI: 73.6%–105.1%). After food, there was a significantly higher C_{max} and $AUC_{0-\infty}$ with nifedipine GITS compared to monolayer osmotic release system with point estimates of 79.6% (90% CI: 70.3%–90.0%) and 81.6% (90% CI: 74.1%–89.7%), respectively. Thus, the monolayer tablet showed a longer lag time in release of drug both in vitro and in vivo as well as a decreased extent of release of drug over a 24-hour dosing interval. This results in a lack of bioequivalence of the monolayer oral osmotic nifedipine tablet when compared to the bilayer osmotic nifedipine GITS tablet.[29]

Clinical studies comparing once-daily nifedipine formulations

A series of clinical studies have established that not only is there a close relationship between plasma concentrations of nifedipine and the corresponding antihypertensive effect of the drug,[8,30] but also that the hemodynamic responses (heart rate and blood pressure) to nifedipine are additionally determined by the rate of delivery of the drug into the systemic circulation.[31] These findings are also compatible with the observation that different formulations of nifedipine have differential effects on the sympathetic nervous system.[32] It is therefore reasonable to postulate that the pharmacokinetic differences in nifedipine disposition observed in a number of bioequivalence studies could result in significant differences in antihypertensive effect and in activation of the sympathetic nervous system.

This postulate was evaluated in a randomized crossover study in 43 older hypertensive patients comparing "branded" nifedipine GITS and an alternative once-daily formulation (mini tablets in a capsule).[33] Peak nifedipine plasma concentrations were achieved at 4 hours after the first dose of the generic, modified-release formulation of nifedipine and at 6 hours after nifedipine GITS. Systolic blood pressure decreased rapidly after the first dose of generic nifedipine, achieving a nadir at 5 hours post-dose accompanied by a slight rise in heart rate. In contrast, after nifedipine GITS, heart rate fell slightly. At the time of peak drug concentration, plasma noradrenaline was higher in patients receiving the modified-release formulation of nifedipine than in those receiving nifedipine GITS, and the increase from baseline was statistically significantly greater with generic nifedipine (Figure 3). Similar differences were seen again at 5 hours after switching formulations during a steady-state treatment period at days 15 and 29. This study suggests that these two different formulations of once-daily nifedipine are not interchangeable since there were significantly different blood pressure and plasma noradrenaline responses. Furthermore, even at steady state, switching between formulations caused opposite effects on the activity of the sympathetic nervous system in response to a fall in blood pressure.[33] It is important to appreciate that these significant differences were detected with repeated measurements over an 8-hour period and would not readily have been detected at conventional, single-time-point clinic visits. Nevertheless, the differences were of sufficient magnitude to suggest that there would be clinically important differences in therapeutic responses in individual patients.

There are only a few additional studies that focus on direct head-to-head comparisons of different once-daily formulations of nifedipine. In a randomized, double-blind study in 91 patients with mild to moderate hypertension, nifedipine GITS 30 mg was compared to a nifedipine formulation composed of microgranules.[17] At the end of 8 weeks, the mean sitting office systolic blood pressure in the microgranule formulation group was 136 mmHg and, in the nifedipine GITS group, 133 mmHg ($P = 0.048$). In another study, a group of 54 hypertensive patients were randomized to a microgranule formulation of nifedipine or nifedipine GITS.[34] At the end of the 12-week study, a 24-hour ambulatory blood pressure measurement was made with average daytime readings in the microgranule group of 109 mmHg compared to 104 mmHg in the nifedipine GITS group. The respective nighttime values were 99 and 96 mmHg.

In a subsequent study, Rodriguez-Roa et al[35] randomized a group of 192 hypertensive patients to either a microgranule formulation of nifedipine or nifedipine GITS and followed them for 8 weeks with ambulatory blood pressure monitoring. The average daytime and nighttime values in the microgranule group were 103 mmHg and 94 mmHg, respectively, with corresponding values of 98 and 101 mmHg in the patients treated with nifedipine GITS.

A more recent, small case report focused on three patients who were switched from nifedipine GITS to an alternative monolayer osmotic pump formulation and had their blood pressure monitored by home blood pressure monitoring.[36] In each case, upon switching, systolic blood pressure increased by more than 8 mmHg. Then, on switching back to nifedipine GITS, blood pressure control was re-established.

The comparative studies are entirely consistent with earlier work on nifedipine that demonstrated the close

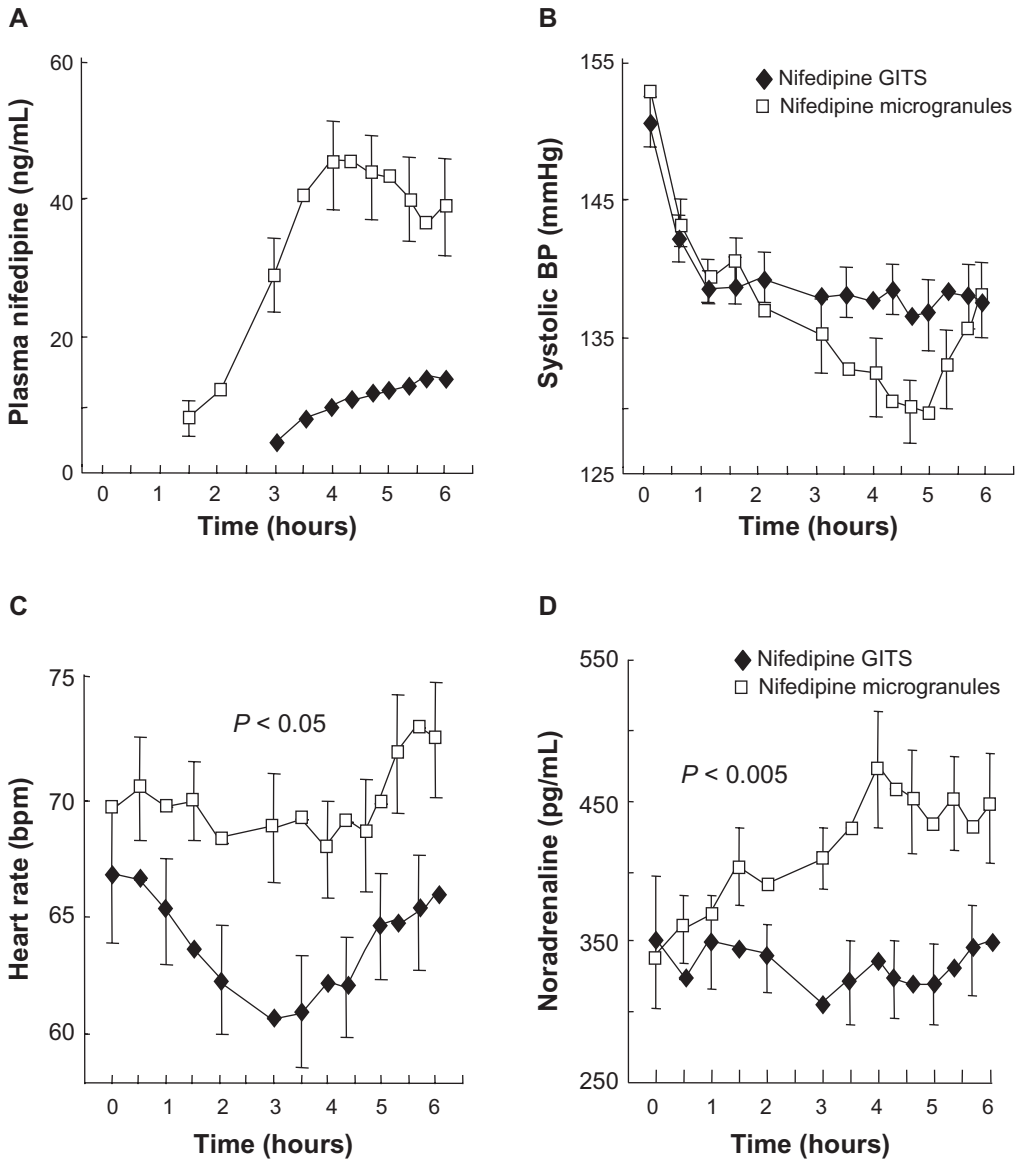

Figure 3 Responses to initiating therapy with different nifedipine formulations. (**A**) Plasma concentrations; (**B**) systolic BP; (**C**) heart rate; (**D**) plasma noradrenaline.

Abbreviations: BP, blood pressure; GITS, gastrointestinal therapeutic system.

relationship between plasma concentration of drug and blood pressure response.[8,30]

Conclusion

There is a compelling volume of evidence to indicate that all once-daily nifedipine formulations are not pharmacokinetically and pharmacodynamically equivalent. Under certain conditions, alternative formulations produce more rapid rises in plasma nifedipine concentrations that lead to more abrupt falls in blood pressure and trigger activation of the sympathetic nervous system. Therefore, considerable caution must be exercised, and interchangeability of different formulations cannot be assumed even if clinical blood pressure control (measured conventionally at a single time point) appears to be similar. This lack of therapeutic equivalence is acknowledged in the UK, where the different once-daily nifedipine formulations are not considered to be interchangeable such that the British National Formulary 65 states that "different versions of modified-release 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."[37]

It would be easy to dismiss the pharmacokinetic and pharmacodynamic differences between different formulations as being practically irrelevant. In reality, however, with respect to cardiovascular disease, it must be recognized that

small differences in blood pressure may equate to significant differences in outcome.[38,39] Thus, differences in blood pressure that would be deemed to be relatively unimportant in an individual would be of considerable importance in a population. This is exemplified in the statistical analysis from the 2006 Health Survey for England, which suggests that, on a population basis, a 2 mmHg reduction in diastolic blood pressure would result in a saving of 14,000 lives per annum in the UK.[40]

In conclusion, therefore, caution must be exercised when assuming that relatively small differences in pharmacokinetics will be inconsequential with respect to pharmacodynamics, therapeutic response, and clinical outcome. In particular, for drugs with a narrow therapeutic index and/or a direct, linear pharmacokinetic–pharmacodynamic relationship, generic substitution (based on conventional bioequivalence criteria or on the class effect) should be considered only when there is robust, additional evidence in support of therapeutic equivalence.

Disclosure

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