ORIGINAL ARTICLE

Long-acting dihydropyridine calcium-channel blockers and sympathetic nervous system activity in hypertension: A literature review comparing amlodipine and nifedipine GITS

COREY B. TOAL¹, PETER A. MEREDITH² & HENRY L. ELLIOTT³

¹Department of Pharmacology, University of Toronto, Toronto, Canada, ²University of Glasgow, Glasgow, UK, and ³University of Strathclyde, Glasgow, UK

Abstract
Calcium-channel blockers (CCBs) constitute a diverse group of compounds but are often referred to as a single homogeneous class of drug and the clinical responses indiscriminately summarized. Even within the dihydropyridine subgroup, there are significant differences in formulations, pharmacokinetics, durations of action and their effects on blood pressure, heart rate, end organs and the sympathetic nervous system. Amlodipine and nifedipine in the gastrointestinal therapeutic system (GITS) formulation are the most studied of the once-daily CCBs. Amlodipine has an inherently long pharmacokinetic half-life, whereas, in contrast, nifedipine has an inherently short half-life but in the GITS formulation the sophisticated delivery system allows for once-daily dosing. This article is derived from a systematic review of the published literature in hypertensive patients. The following search terms in three main databases (MEDLINE, Embase, Science Citation Index) from 1990 to 2011 were utilized: amlodipine, nifedipine, sympathetic nervous system, sympathetic response, sympathetic nerve activity, noradrenaline, norepinephrine and heart rate. More than 1500 articles were then screened to derive the relevant analysis. As markers of sympathetic nervous system activation, studies of plasma norepinephrine concentrations, power spectral analysis, muscle sympathetic nerve activity and norepinephrine spillover were reviewed. Overall, each drug lowered blood pressure in hypertensive patients in association with only small changes in heart rate (i.e. /beat/min). Plasma norepinephrine concentrations, as the most widely reported marker of sympathetic nervous system activity, showed greater increases in patients treated with amlodipine than with nifedipine GITS. The evidence indicates that both these once-daily dihydropyridine CCBs lower blood pressure effectively with minimal effects on heart rate. There are small differences between the drugs in the extent to which each activates the sympathetic nervous system with an overall non-significant trend in favour of nifedipine GITS.

Key Words: Amlodipine, blood pressure, catecholamines, extended release, GITS, nifedipine, norepinephrine, sympathetic activation, sympathetic nerve activity

Introduction
Calcium-channel blockers (CCBs), comprise three distinct subgroups: benzothiazepines (e.g. diltiazem), dihydropyridines (e.g. amlodipine, nifedipine) and phenylalkylamines (e.g. verapamil). Despite this diversity, they are often referred to as a single, homogeneous class of pharmacological agents. Furthermore, even within the dihydropyridine group, there are numerous drugs and formulations (e.g. nifedipine capsules, retard, gastrointestinal therapeutic system: GITS) with different pharmacokinetic profiles, clinical uses and responses, and different dosing requirements.

Despite these various pharmacokinetic differences, arterial vasodilatation is the fundamental response to calcium-channel blockade with a dihydropyridine CCB. Peripheral arterial vasodilatation leads to a reduction in blood pressure and coronary artery vasodilatation leads to increased blood flow to the myocardium. However, it has long been known that potent arterial vasodilators evoke a baroreceptor-mediated reflex increase in heart rate that is
mediated via the sympathetic nervous system. This holds for both arterial vasodilators, such as nifedipine and hydralazine (1), and for mixed arterio-venous dilators such as nitroglycerin (2). Thus, the positive consequences of arterial vasodilatation may be compromised by activation of the sympathetic nervous system and an increase in heart rate.

Insights into the balance between these positive and negative effects became apparent in the results of the early studies with nifedipine in its immediate release formulation: two clinical outcome studies indicated that in patients with unstable angina (3) and post-myocardial infarction (4), the administration of nifedipine, as a potent arterial vasodilator, did not lead to a clear reduction in morbidity and mortality. At the time, this appeared counter-intuitive because coronary vasodilatation in both these conditions would be expected to increase oxygen delivery to the myocardium and benefit the patients, as would the reduction in cardiac work through the reduction in afterload. However, in hindsight, reflex sympathetic activation, catecholamine release and increased heart rate would be likely to have offset the expected beneficial effect.

In a later review, Grossman & Messerli (5) suggested that rapid-onset, short-acting dihydropyridine CCBs evoked sympathetic activation, whether administered acutely or over several weeks. In contrast, long-acting dihydropyridine CCBs did not evoke the same response. However, this is an over-simplification: for example, the once-daily ER formulation of the dihydropyridine drug felodipine has been shown to elevate plasma catecholamines (a marker of sympathetic activation) and result in less left ventricular regression in hypertensive patients compared with either enalapril or nifedipine GITS (6,7).

Despite obvious differences between drugs, between classes or subgroups or formulations, CCBs are often indiscriminately grouped together. They are often summarized as a single entity in reviews of outcome trials and when reviewed by formulary committees and by funding organizations. This raises obvious questions about the most appropriate method of considering the interchangeability of different CCBs and, for this reason, we decided to conduct a detailed review of the literature on two of the most commonly used dihydropyridine CCBs, amlodipine and nifedipine GITS, with specific regard to their effects on sympathetic activation.

Methods

Literature review

The MEDLINE (Pubmed), Embase, Derwent Drug File, Biosis and Science Citation Index databases were searched for articles published between 1990 and April 2011 on amlodipine and nifedipine using the terms sympathetic nervous system, sympathetic response, sympathetic nerve activity, noradrenaline, norepinephrine, heart rate, hypertension. We included only articles published in the English language. If a study was published in more than one journal, efforts were made only to include the data once from whichever article was most complete in study details and data. The primary focus was on full manuscript publications and not abstracts. However, if an abstract was published but a full paper was not subsequently found, the abstract was used if there were data on number of patients, dose of drug, duration of treatment and relevant measurement values. More than 1500 articles were screened and only those in which treatment lasted for at least 1 week were included in the analysis.

Indices of sympathetic nervous system activity

The following measurements of sympathetic nervous system activity/sympathetic activation were evaluated:

1. plasma norepinephrine (noradrenaline) concentrations;
2. muscle sympathetic nerve activity recordings;
3. power spectral analyses of low-frequency and high-frequency activity.

All plasma concentration values for norepinephrine were converted to pg/ml and changes were calculated as percentage (%) values. Sympathetic activation values were included for patients at rest as distinct from those stimulated by mental stress, handgrip, standing or cold pressor tests.

Background details

Generally, data were reported for patients in the supine or sitting position. For the blood pressure measurements, office- or clinic-based values are incorporated and average daytime values if ambulatory blood pressure readings were used. If the final blood pressure, heart rate or other measurement was not given as an absolute value but as a change from baseline, the end of measurement value was calculated by simply adding the mean change value to the initial/baseline value. To make allowances for different baseline values, different study designs, different methodologies etc., percentage changes from baseline to the end time point have been calculated. If measurements were made at multiple time points within one published study, the longest duration of treatment was chosen and if multiple doses were reported, or dose titration occurred, the final dose of drug or the most-used dose is reported.

Statistics

Only one study permitted a direct statistical comparison (8). It was adjudged that formal statistical testing was not otherwise appropriate because of wide variability in the results and because of significant differences in
methodologies, study characteristics and relatively small study numbers. Thus, summary statistics (means, standard error and percentage change) were used to make comparisons between the drugs.

Results

Plasma norepinephrine

Measurement of plasma norepinephrine concentrations was the most commonly reported index of sympathetic activity and activation. Twenty-three (23) studies were identified for amiodipine and 14 (14) for nifedipine GITS. For amiodipine, 698 patients were evaluated with an overall mean age of 56 years (Table I). Corresponding mean values for nifedipine GITS were 291 patients and 57 years (Table II). There was considerable variability in the plasma norepinephrine results in that the changes from baseline ranged from −21.4% to 55.6% with amiodipine and from −3.1% to 58.9% with nifedipine GITS.

The changes in blood pressure (BP) and heart rate were similar with the two drugs. With amiodipine, systolic blood pressure (SBP) decreased by 10.2 ± 0.9%, diastolic blood pressure (DBP) by 10.4 ± 0.8% and heart rate increased by 0.6 ± 0.8% (Table I). With nifedipine GITS, the respective changes were 10.9 ± 1.7%, 12.0 ± 1.6% and 0.7 ± 0.9% (Table II).

In summary, plasma norepinephrine increased by 21.7 ± 4.3% after amiodipine and by 17.1 ± 5.7% after nifedipine GITS (Figure 1).

Muscle sympathetic nerve activity

Measurement of muscle (peroneal nerve) sympathetic activity was the second most commonly used method and was employed in five amiodipine studies and in one study with nifedipine GITS. In the amiodipine studies, a total of 70 patients with an average age of 52 years were evaluated (Table III). For nifedipine GITS, the single small study split the 18 patients into older and younger groups for evaluation but the overall mean age was similar at 56 years (Table III).

The changes in SBP, DBP and heart rate were 8.4 ± 1.0%, 6.7 ± 1.0% and 0.4 ± 2.2%, respectively, in the amiodipine studies and the corresponding values were 3.8 ± 3.0%, 4.5 ± 3.5% and 3.0 ± 0.1% in the nifedipine studies.

In summary, the increase in muscle sympathetic nerve activity was 21.4 ± 8.5% for amiodipine and 6.7 ± 1.8% for nifedipine GITS (Figure 2).

Power spectral analysis

This methodology involves continuous measurement of the ECG to tease out R–R interval variations using

Table I. Studies on amiodipine reporting plasma norepinephrine.

| Reference       | Year | n   | Mean age (years) | Dose (mg) | Time interval (weeks) | Δ in SBP | Δ in DBP | Δ in HR | Δ in NE |
|-----------------|------|-----|------------------|-----------|----------------------|---------|---------|---------|---------|
| Lopez et al.    | 1990 | 12  | 61               | 2.5–10    | 4                    | −8.1    | −8.9    | 35.1    |
| Donati et al.   | 1992 | 10  | 47               | 5         | 8                    | −11.3   | −9.3    | −5.6    | −8.7    |
| Leenen and Fourney | 1996 | 17  | 55               | 10        | 26                   | −13.3   | −12.7   | −11.1   |
| Sasaguri et al. | 1997 | 8   | 5                | 1         | 1                    | −13.2   | −8.8    | 1.2     | 3.0     |
| Hamada et al.   | 1998 | 16  | 60               | 5         | 4                    | −10.5   | −7.2    | −1.4    | −21.4   |
| de Champlain et al | 1998 | 22  | 55               | 10        | 6                    | −10.0   | −12.6   | 8.0     | 55.6    |
| Sakata et al.   | 1999 | 24  | 63               | 10        | 12                   | −17.7   | −20.2   | 0.0     | 18.9    |
| Malamani et al. | 1999 | 60  | 10               | 12        |                      | −7.9    | −8.9    | 4.1     | 1.4     |
| Spence et al.   | 2000 | 24  | 47               | 10        | 4                    | −9.8    | −9.0    | 1.5     | 23.2    |
| Fogari et al.   | 2000 | 15  | 55               | 10        | 24                   | −11.9   | −13.7   | 1.4     | 34.9    |
| Lefrandt et al. | 2001 | 145 | 51               | 5         | 8                    | −9.8    | −9.0    | 1.5     | 23.2    |
| Struck et al.   | 2002 | 18  | 56               | 5         | 1                    | −9.1    | −5.3    | 6.0     | 33.7    |
| Eguchi et al.   | 2002 | 46  | 69               | 10        | 8                    | −17.3   | −10.9   | −2.9    | 23.8    |
| Binggeli et al. | 2002 | 14  | 58               | 5         | 8                    | −9.7    | −9.6    | −4.6    | 47.1    |
| Ohbayashi et al.| 2003 | 37  | 68               | 5         | 26                   | −1.4    | −1.3    | 0.0     | 13.0    |
| Malacco et al.  | 2004 | 46  | 57               | 10        | 12                   | −9.8    | −12.6   | 2.7     | 15.2    |
| Karas et al.    | 2005 | 22  | 57               | 10        | 8                    | −14.3   | −12.0   | 2.7     | 48.8    |
| Leenen et al.   | 2006 | 29  | 41               | 5         | 8                    | −4.4    | −15.1   | 19.3    |
| Leenen et al.   | 2006 | 37  | 67               | 5         | 8                    | −0.7    | −11.4   | 7.4     |
| Ruzicka et al.  | 2007 | 10  | 42               | 5         | 6                    | −4.6    | −4.4    | −2.7    | 18.6    |
| de Champlain et al | 2007 | 23  | 57               | 10        | 8                    | −12.8   | −12.4   | 1.4     | 38.2    |
| Larochelle et al.| 2008 | 42  | 58               | 10        | 8                    | −12.3   | −11.6   | 8.1     | 38.1    |
| Sanjuliani et al.| 2002 | 21  | 47               | 10        | 26                   | −15.2   | −3.6    |
| Total           |      | 698 |                  |           |                      |         |         |         |

Mean 55.8

Mean % change −10.2 −10.4 0.6 21.7

SE 0.94 0.83 0.78 4.27

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; NE, norepinephrine; %Δ, percentage change. a Each reference is an independent study published reporting on the relevant parameters indicated with % changes calculated on the group means.
fast Fourier transformation and autoregressive algorithms (9). The low-frequency component of the power spectrum is an indicator of sympathetic nerve activity to the heart and high-frequency activity is a measure of parasympathetic activity. Ten studies on amlodipine in hypertensive patients looked at these measures. The average age of the 180 patients studied was 54 years (Table IV). There were no such studies with nifedipine GITS.

In the amlodipine-treated patients, the decreases in SBP, DBP and heart rate were 13.5 ± 1.8%, 10.8 ± 1.0% and 1.0 ± 1.3% (Table IV). The low-frequency component of the power spectrum decreased by 3.3 ± 7.5%, the high-frequency component increased by 6.2 ± 6.6% and the ratio of low to high frequency increased by 11.9 ± 12.6% (Figure 3).

Discussion

The activity of the sympathetic nervous system is essential for the moment-to-moment regulation of the cardiovascular system but “overactivity” has been implicated in both the genesis of, and the complications of, cardiovascular disease (10,11). With regard to treatment effects, specifically with dihydropyridine CCBs, it has been reported that the short-acting and long-acting drugs have distinctly different effects on the sympathetic nervous system. Thus, formulations of dihydropyridine CCBs, which result in a steep rise in plasma drug concentrations, have been shown to activate the sympathetic nervous system, e.g. nifedipine capsule, nifedipine retard or felodipine (7,8,12–14). In summary, sympathetic activation is typically seen with short-acting dihydropyridine CCBs but the fundamental factor is rapid-onset vasodilatation.

In the earlier review by Grossman & Messerli (5), long-acting agents were indiscriminately grouped together. This present overview compares the evidence derived in studies of the two established long-acting, once-daily dihydropyridine CCBs, which have the greatest volume of clinical outcome evidence: amlodipine an agent with an intrinsically long pharmacokinetic elimination half-life and nifedipine GITS, a high-tech osmotic delivery system, which confers extended release characteristics (15).
Unfortunately, there is only one study that directly compares amlodipine and nifedipine GITS: the conclusion of this single study was that chronic treatment with amlodipine was associated with sympathetic activation, whereas no such activation occurred with nifedipine GITS. This finding is consistent with the overall trend in this present analysis albeit there was no statistical significance. However, the changes in baseline for plasma norepinephrine do not appear to be directly related to the blood pressure lowering effect, since the blood pressure decreases were very similar between the two drugs with, if anything, a marginally greater decrease with nifedipine GITS. Furthermore, the heart rate changes were comparable with the two drugs at approximately 0.6 beats/min.

Thus, the main finding of this overview is that amlodipine (despite its “positive” profile in clinical outcome studies) caused a small but significant activation of the sympathetic nervous system, as assessed by multiple markers. It is also noteworthy that, for measurements of plasma norepinephrine and assessment of muscle sympathetic activation, the percentage increases are coincidentally almost identical (i.e. 21.7% and 21.4%, respectively). In turn, the ratio of low to high frequency from the power spectral analysis suggests that the sympathetic activation component overall is greater than the parasympathetic component after amlodipine administration. Therefore, there is consistency in three different surrogate measures for sympathetic activation, suggesting that amlodipine increases activity of the sympathetic nervous system in hypertensive patients.

A detailed explanation for the apparent differential effects of amlodipine and nifedipine GITS on the sympathetic nervous system is not readily apparent. However, in studies of spontaneously hypertensive rats (SHR), Huang & Leenen (16) concluded that, even during chronic amlodipine administration, there was a balance between peripheral effects and central effects, whereby the plasma concentration of drug might influence the activation of the sympathetic nervous system. Similar results were obtained in a study with nifedipine in SHR (17). However, a slow peripheral intravenous infusion of nifedipine in SHR resulted in a sympatho-inhibitory response – decrease in blood pressure, renal sympathetic nerve activity and heart rate. The GITS osmotic delivery system with nifedipine may be thought to mimic more closely a slow infusion of drug (relative to other formulations e.g. capsules, Retard) and explain to some degree the more neutral effects seen with nifedipine GITS compared with previous formulations. Taken together, these studies with amlodipine and nifedipine GITS suggest that BP reduction and the effects on the sympathetic

Table III. Studies on amlodipine and nifedipine gastrointestinal therapeutic system (GITS) reporting muscle sympathetic nerve activity.

| Reference* | Year | n  | Mean age (years) | Dose (mg) | Time interval (weeks) | Δ% in SBP | Δ% in DBP | Δ% in HR | Δ% in MSA |
|------------|------|----|-----------------|----------|----------------------|-----------|----------|---------|----------|
| Amlodipine |      |    |                 |          |                      |           |          |         |          |
| Calhoun (52) | 1997 | 10 | 47              | 10       | 4                    | −9.6      | −7.6     | 2.9     | 40.0     |
| Binggeli et al. (32) | 2002 | 14 | 58              | 5        | 8                    | −9.7      | −9.6     | −4.6    | 6.1      |
| Struck et al. (30) | 2002 | 18 | 56              | 5        | 1                    | −9.1      |          |         |          |
| Ruzicka et al. (37) | 2007 | 10 | 42              | 5        | 6                    | −4.6      | −4.4     | −2.7    | −3.9     |
| Dodt et al. (53) | 2000 | 18 | 56              | 5        | 1                    | −9.1      | −5.3     | 6.0     | 32.6     |
| Total       |      |    |                 |          |                      | −8.4      | −6.7     | 0.4     | 21.4     |
| Mean        |      | 51.8|                 |          |                      | 0.97      | 1.04     | 2.19    | 8.54     |
| Nifedipine GITS |     |    |                 |          |                      |           |          |         |          |
| Ruzicka et al. (49) | 2004 | 10 | 45              | 20       | 4                    | −0.76     | −1.012   | 2.94    | 4.88     |
| Ruzicka et al. (49) | 2004 | 8  | 67              | 20       | 4                    | −6.85     | −8.05    | 3.08    | 8.51     |
| Total       |      | 56 |                 |          |                      | −3.81     | −4.53    | 3.01    | 6.69     |
| Mean        |      | 56 |                 |          |                      | 3.04      | 3.52     | 0.07    | 1.82     |

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; MSA, muscle sympathetic nerve activity; Δ%, percentage change. *Each reference is an independent study published reporting on the relevant parameters indicated with % changes calculated on the group means.

Figure 2. The effects of amlodipine on systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) and muscle sympathetic nerve activity (MSA) when the drug is given over weeks of treatment. This figure is based on the mean percentage changes from Table III for all the studies cited.
assessments should provide more robust data. To date, ideally a study comparing the two drugs in a head-to-head manner with proper randomization and confounding factors when trying to compare drugs.

Results All of these are potentially complicating and age of patient etc. Moreover, no formal statistical measurements, time of day, body posture, dose of drug, durations of hypertension, severity of disease, baseline blood pressures, conditions for sampling or meanings in the pathogenesis of hypertension and its cardiovascular complications. However, both amlodipine and nifedipine GITS have positive outcome data in the treatment of hypertensive patients (i.e. ALLHAT, INSIGHT respectively (18,19)). This suggests that there is a balance between the benefits of lowering blood pressure and the potentially adverse consequences of sympathetic activation.

 Ideally, a study comparing the two drugs in a head-to-head manner with proper randomization and assessment should provide more robust data. To date, only one such study was found, that by de Champlain et al. (8). In that study, although amlodipine did not result in a transient rise in plasma norepinephrine after either acute or chronic dosing, administration for 6 weeks was reported to cause a 50% increase in the overall basal concentration of plasma norepinephrine. This was not observed with nifedipine GITS.

Chronic activation of the sympathetic nervous system has been implicated in the pathogenesis of hypertension and its cardiovascular complications. However, both amlodipine and nifedipine GITS have positive outcome data in the treatment of hypertensive patients (i.e. ALLHAT, INSIGHT respectively (18,19)). This suggests that there is a balance between the benefits of lowering blood pressure and the potentially adverse consequences of sympathetic activation.

In practice, therefore, effective BP reduction may be more important than modest sympathetic activation. There are additional considerations, the most obvious of which is that many patients require multiple drugs to manage their blood pressure and the interaction of these other drugs in conjunction with the CCBs may have some counterbalancing effect. Overall, despite the view fostered by the major hypertension treatment guidelines, it is apparent that the dihydropyridine CCBs cannot be considered a homogenous group of compounds. Furthermore, even two long-acting once-a-day drugs like amlodipine and nifedipine GITS, with similar clinical profiles, may have both qualitatively and quantitatively different effects on the sympathetic nervous system.

Acknowledgements

The publication of this article has been supported by an unrestricted grant from Bayer AG.
Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Murphy MB, Scriven AJ, Brown MJ, Causon R, Dollery CT. The effects of nifedipine and hydralazine induced hypotension on sympathetic activity. Eur J Clin Pharmacol. 1982;23:479–482.

2. Curry SH, Lopez LM, Lambert CR, Kwon HR, Stack RK. Plasma concentrations and hemodynamic effects of intravenous, sublingual, and aerosolized nitroglycerin in patients undergoing cardiac catheterization. Biopharm Drug Dispos. 1993;14:107–118.

3. Lubes J, Tijssen JGP, Kerkhamp HJ. Early treatment of unstable angina in the coronary care unit: A randomized, double blind, placebo controlled comparison of recurrent ischaemia in patients treated with nifedipine of metoprolol or both. Br Heart J. 1986;56:400–413.

4. Behar S. Secondary prevention reinfarction Israeli nifedipine trial (SPRINT). A randomized intervention trial of nifedipine in patients with acute myocardial infarction. Eur Heart J. 1988;9:354–364.

5. Grossman E, Messerli FH. Effect of calcium antagonists on plasma norepinephrine levels, heart rate, and blood pressure. Am J Cardiol. 1997;80:1453–1458.

6. Leenen FH, Hollis DL. Antihypertensive effect of felodipine associated with persistent sympathetic activation and minimal regression of left ventricular hypertrophy. Am J Cardiol. 1992;69:639–645.

7. Leenen FHH, Myers MG, Joyner CD, Toal CB. Differential effects of once-daily antihypertensive drugs on blood pressure, left ventricular mass and sympathetic activity: Nifedipine-GITS versus felodipine-ER versus enalapril. Can J Cardiol. 2002;18:1285–1293.

8. de Champlain J, Karras M, Nguyen P, Cartier P, Wistaff R, Toal CB, Nadeau R, Larochelle P. Different effects of nifedipine and amlopidine on circulating catecholamine levels in essential hypertensive patients. J Hypertens. 1998;16:1357–1369.

9. Pagani M, Lombardi F, Guzzetti S, Rimoldi O, Furlan R, Pizzinelli P, Sandrone G, Malfatto G, Dell’Orto S, Piccaluga G. Power spectral analysis of heart rate and arterial pressure variables as a marker of sympatho-vagal interaction in man and dog. Circ Res. 1986;59:178–193.

10. Julius S. Sympathetic hyperactivity and coronary risk in hypertension. Hypertension. 1993;21:886–893.

11. Palatini P, Julius S. Heart rate and the cardiovascular risk. J Hypertens. 1997;15:3–17.

12. Kleinbloesem CH, van Brummelen P, van de Linde JA, Voogd PJ, Breimer DD. Nifedipine: Kinetics and dynamics in healthy subjects. Clin Pharmacol Ther. 1984;35:742–749.

13. Kleinbloesem CH, van Herten J, de Leeve LGJ, van Brummelen P, Breimer DD. Nifedipine kinetics and dynamics during rectal infusion to steady state with an osmotic system. Clin Pharmacol Ther. 1984;36:396–401.

14. Myers MG., Raemisch K. D. Comparative pharmacokinetics and antihypertensive effects of the nifedipine tablet and capsule. J Cardiovasc Pharmacol. 1987;10 Suppl 10:S76–S78.

15. Toal CB, Meredith PA, Elliott HL. Once Daily Nifedipine: The formulation dictates the pharmacokinetic characteristics and the therapeutic responses. Int J Clin Pharmacol. 2012;50:202–217.

16. Huang BS, Leenen FHH. Sympathoinhibitory and depressor effects of amlopidine in spontaneously hypertensive rats. J Cardiovasc Pharmacol. 2003;42:153–160.

17. Murzenok PP, Huang BS, Leenen FHH. Sympathoinhibition by central and peripheral infusion of nifedipine in spontaneously hypertensive rats. Hypertension. 2000;35:631–636.

18. ALLHAT Officers and Coordinators. Major outcomes in high risk hypertensive patients randomized to angiotensin converting enzyme inhibitor or calcium channel blocker vs diuretic: The antihypertensive and lipid lowering treatment to prevent heart attack trial (ALLHAT). JAMA. 2002;288:2981–2997.

19. Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, Mancia G, Rosenthal, T, Ruilope LM. 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;356:366–372.

20. Lopez LM, Thorman AD, Mehta JL. Effects of amlopidine on blood pressure, heart rate, catecholamines, lipid responses and adrenergic stimulus. Am J Cardiol. 1990;66:1269–1271.

21. Donati L, Buhler FR, Beretta-Piccoli C, Kusch F, Heinen G. Antihypertensive mechanism of amlopidine in essential hypertension: Role of pressor reactivity to norepinephrine and Angiotensin II. Clin Pharmacol Ther. 1992;52:50–59.

22. Leenen FHH, Fournier A. Comparison of the effects of amlopidine and diltiazem on 24-hour blood pressure, plasma catecholamines, and left ventricular mass. Am J Cardiol. 1996;78:203–207.

23. Sasaguri M, Matsumoto N, Noda K, Koga M, Kinoshita A, Ideishi M, Arakawa K. Amlopidine lowers blood pressure without increasing sympathetic activity or activating the renin–angiotensin system in patients with essential hypertension. Eur J Clin Pharmacol. 1997;53:197–201.

24. Hamada T, Watanabe M, Kanaeda T, Ohtahara A, Kinugawa T, Hisatome I, Fujimoto Y, Yoshida A, Shigemasa C. Evaluation of changes in sympathetic nerve activity and heart rate in essential hypertensive patients induced by amlopidine and nifedipine. J Hypertens. 1998;16:111–118.

25. Sakata K, Shirotani M, Yoshida H, Nawada R, Ohayashi K, Toggi K, Mihm N. Effects of Amlodipine and Cilnidipine on cardiac sympathetic nervous system and neurohormonal status in essential hypertension. Hypertension. 1999;33:1447–1452.

26. Malamani GD, Corradi L, Zoppì A, Mugellini A, Preti P, Mennoia VN, Finardi G, Fogari R. Effects of different dihydropyridine calcium antagonists on plasma norepinephrine in essential hypertension. J Hypertens. 1999;17 Suppl 3:S134.

27. Spence JD, Munoz C, Huff MW, Tokmakjian S. Effect of amlopidine on hemodynamic and endocrine responses to mental stress. Am J Hypertens. 2000;13:518–522.

28. Fogari R, Zoppì A, Corradi L, Preti P, Malamani GD, Mugellini A. Effects of different dihydropyridine calcium antagonists on plasma norepinephrine in essential hypertension. J Hypertens. 2000;18:1871–1875.

29. Lefrandt JD, Heinmann J, Sever K, Castellan M, Hausberg M, Fallon M, Uribiguit, A, Restrup M, Agabiti-Rosei E, Rahn KH, Murphy M, Zannad P, de Kam PJ, Smit AJ. Con- trasting effects of verapamil and amlopidine on cardiovascular stress responses in hypertension. J Clin Pharmacol. 2001; 51:687–692.

30. Streuck J, Muck P, Trubger D, Handrock R, Weidinger G, Dendorfer A, Dodt C. Effects of selective angiotensin II receptor blockade on sympathetic nerve activity in primary hypertensive subjects. J Hypertens. 2002;20:1143–1149.

31. Eguchi K, Kario K, Shimada K. Differential effects of a long-acting angiotensin converting enzyme inhibitor (temocapril) and a long-acting calcium antagonist (amlodipine) on ven- tricular ectopic beats in older hypertensive patients. Hypertension. 2002;39:892–896.

32. Bingelli C, Corti R, Sudano I, Luscher TF, Noll G. Effects of chronic calcium channel blockade on sympathetic nerve activity in hypertension. Hypertension. 2002;39:892–896.

33. Ohbayashi Y, Tsutamoto T, Sakaguchi T, Tanaka T, Kanamori T, Yokohama H, et al. Effect of an angiotensin II Type 1 receptor blocker, Valsartan, on neurohumoral factors in patients undergoing cardiac catheterization. Biopharm Drug Dispos. 1993;14:107–118.

34. Toal CB, Meredith PA, Elliott HL. Once Daily Nifedipine: The formulation dictates the pharmacokinetic characteristics and the therapeutic responses. Int J Clin Pharmacol. 2012;50:202–217.
with hypertension: Comparison with a long-acting calcium channel antagonist, amlodipine. J Cardiovasc Pharmacol. 2003;42 Suppl 1:S71–S74.

34. Malacco E, Piazza S, Scandiani L, Zoppi A. Effects of valsartan/hydrochlorothiazide and amlodipine on ambulatory blood pressure and plasma norepinephrine levels in high-risk hypertensive patients. Adv Ther. 2004;21:149–161.

35. Karas M, Lacourciere Y, LeBlanc AR, Nadeau R, Dube B, Florescu M, et al. Effect of the renin–angiotensin system or calcium channel blockade on the circadian variation of heart rate variability, blood pressure and circulating catecholamines in hypertensive patients. J Hypertens. 2005;23:1251–1260.

36. Leenen FHJ, Coletta E, White R. Sympatho-excitatory responses to once-daily dihydropyridines in young versus older hypertensive patients: amlodipine versus felodipine extended release. J Hypertens. 2006;24:177–184.

37. Ruzicka M, Coletta E, Leenen FHJ. Does blockade of the renin angiotensin system affect sympathetic and blood pressure responses to amlodipine in young hypertensive patients? Am J Hypertens. 2007;20:1202–1208.

38. de Champlain J, Karas M, Assouline L, Nadeau R, LeBlanc R, Dube B, et al. Effects of valsartan or amlodipine alone or in combination on plasma catecholamine levels at rest and during standing in hypertensive patients. J Clin Hypertens. 2007;9:168–178.

39. Larochelle P, Karas M, Lamarre-Cliché M, Lacourciere Y, de Champlain. Effect of 8 weeks administration of antihypertensive agent on plasma catecholamines, renin and aldosterone in patients with essential hypertension. J Hypertens. 2008;26 Suppl 1:S462.

40. Sanjuliani AF, Genelhu-Fagunde V, Barroso SG, Duarte AVB, Rodrigues MLG, Castro RSP, et al. Effect of an imidazoline agonist on sympathetic activity and components of the insulin resistance syndrome in obese hypertensive Brazilian patients. J Hypertens. 2002;20 Suppl 4:S206.

41. Frohlich ED, McLoughlin MJ, Losem CJ, Ketelhut R, Messerli FH. Hemodynamic comparison of two nifedipine formulations in patients with essential hypertension. Am J Cardiol. 1991;66:1346–1350.

42. Philips RA, Ardeljan M, Shimabukuro S, Goldman ME, Garbowit DL, Eison HB, Krakoff LR. Effects of nifedipine-GITS on left ventricular mass and left ventricular filling. J Cardiovasc Pharmacol. 1992;19 Suppl 2:S28–S34.

43. Halperin AK, Icenogle MV, Kapsner CO, Chick TW, Roehnert J, Murata GH. A comparison of the effects of nifedipine and verapamil on exercise performance in patients with mild to moderate hypertension. Am J Hypertens. 1993;6:1025–1032.

44. DeQuattro V, Lee D. Equivalent reduction of proteinuria in hypertensives by either nifedipine GITS or enalapril: Disparate effects on neurohormones and ambulatory blood pressure and the influence of salt. Cardiology. 1997;88 Suppl 3:38–42.

45. James MA, Rakicka H, Panerai RB, Porter JF. Baroreflex sensitivity changes with calcium antagonist therapy in elderly subjects with isolated systolic hypertension. J Human Hypertens. 1999;13:87–95.

46. Pellizzer A, Kamen PW, Esler MD, Lim S, Krum H. Comparative effects of mibefradil and nifedipine gastrointestinal therapeutic system on autonomic function in patients with mild to moderate essential hypertension. J Hypertens. 2001;19:279–285.

47. Diamond JA, Krakoff LR, Goldman A, Coplan N, Gharavi A, Martin K, et al. Comparison of two calcium blockers on hemodynamics, left ventricular mass, and coronary vasodilatory in advanced hypertension. Am J Hypertens. 2001;14:231–240.

48. Fogari R, Mugellini A, Zoppi A, Corradi L, Rinaldi A, Derosa G, et al. Differential effects of lercanidipine and nifedipine GITS on plasma norepinephrine in chronic treatment of hypertension. Am J Hypertens. 2003;16:596–599.

49. Ruzicka M, Coletta E, Floras J, Leenen FHJ. Effects of low-dose nifedipine GITS on sympathetic activity in young and older patients with hypertension. J Hypertens. 2004;22:1039–1044.

50. Fogari R, Preti P, Zoppi A, Corradi L, Pasotti C, Rinaldi A, et al. Effect of telmisartan/hydrochlorothiazide combination versus nifedipine GITS on ambulatory blood pressure and sympathetic activation. Am J Hypertens. 2005;18:577–583.

51. Brown MJ, Toal CB. Formulation of long-acting nifedipine tablets influences the heart rate and sympathetic nervous system response in hypertensive patients. Br J Clin Pharmacol. 2007;65:646–652.

52. Calhoun DA. Effects of 4 weeks of amlodipine therapy on muscle sympathetic nerve activity. Journal of Investigative Medicine. 1997;70A.

53. Dodt C, Struck J, Muck P, Trubger D, Handrock R, Weidinger G, et al. Different effects of valsartan and amlodipine on muscle sympathetic activity in hypertensive subjects. J Hypertens. 2000;18 Suppl 4:S29.

54. Minami J, Ishimitsu T, Kawano Y, Matsuoka H. Effects of amlodipine and nifedipine retard on autonomic nerve activity in hypertensive patients. Clin Exp Pharmacol Physiol. 1998;25:572–576.

55. Lucini D, Strappazzon P, Milani RV, Messerli FH, Pagani M. Improved baroreflex control in hypertensive patients treated with amlodipine. J Hypertens. 1998;17 Suppl 3:S23.

56. Siche JP, Baguet JP, Fagret D, Tremel F, de Gaudemaris R, Mallion J. Effects of amlodipine on baroreflex and sympathetic nervous system activity in mild-to-moderate hypertension. Am J Hypertens. 2001;14:424–428.

57. Sahin I, Kosat F, Altunkan S, Gunaydin M. Comparison of the effects of amlodipine and verapamil on autonomic nerve activity in hypertensive patients. Eur J Internal Med. 2004;15:225–230.

58. Bilge AK, Atilgan D, Tukek T, Ozcan M, Ozben B, Koylan N, Meric M. Effects of amlodipine and fosinopril on heart rate variability and left ventricular mass in mild-to-moderate essential hypertension. Int J Clin Pract. 2005;59:306–310.

59. Lindqvist M, Kahan T, Melcher A, Ekhholm M, Hjemdahl P. Long-term calcium antagonist treatment of human hypertension with mibefradil or amlodipine increases sympathetic nerve activity. J Hypertens. 2007;25:169–175.