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Comparative effects of felodipine, nitrendipine and nifedipine in healthy subjects: concentration-effect relationships of racemic drugs and enantiomers*

P. A. Soons[1], A. F. Cohen[2], and D. D. Breimer[1]**

[1] Center for Bio-Pharmaceutical Sciences, Division of Pharmacology, University of Leiden, Leiden, The Netherlands
[2] Centre for Human Drug Research, Leiden, The Netherlands

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Summary. The effects of racemic *(rac)* felodipine, *rac*-nitrendipine and nifedipine (all 20 mg solution p.o.) on non-invasively measured blood pressure and heart rate were investigated in a randomised, double-blind, cross-over study in 12 normotensive, young, healthy males. Compared to baseline values, heart rate increased more after *rac*-felodipine treatment (+47% at maximum) than *rac*-nitrendipine (+40%) and nifedipine (+38%); only small and variable changes in blood pressure were observed with any of the drugs. The baseline-corrected area under the heart rate-time curve up to 4 h after the administration of *rac*-felodipine was 197% and 180% larger than after nifedipine and *rac*-nitrendipine treatment, respectively. The effects on heart rate could be fitted individually to a sigmoidal E_{max}-model without hysteresis for all drugs under investigation. The relative potencies of the unbound drugs for their indirect effects on heart rate were 1:7:43 for nifedipine, *rac*-nitrendipine and *rac*-felodipine, respectively. The active (S)-enantiomers of felodipine and nitrendipine appeared to be 9- and 60-times as potent as nifedipine in this respect, assuming no (inter)activity of the (R)-enantiomers. Individual and mean changes in blood pressure were small, they were not related to plasma concentrations, and did not differ between treatments.

Key words: Felodipine, Nitrendipine, Nifedipine; enantiomers, blood pressure, heart rate, concentration-effect relationship, healthy volunteers

Dihydropyridine calcium entry blockers are widely used in the treatment of hypertension and angina pectoris, and members of this class of drugs share many molecular pharmacological and pharmacokinetic characteristics [1, 2]. The relationship between the plasma concentration and haemodynamic effects, especially reflex tachycardia, in normotensive subjects has been reported for nifedipine [3–9], racemic *(rac)* felodipine [10] and *rac*-nitrendipine [5, 11], as well as for other chiral dihydropyridines. Pharmacokinetic-pharmacodynamic modelling of drug effects in healthy subjects is of interest in order to make better use of information obtained during early drug development [12–14]. For example, the concentration-effect relationship of nifedipine in healthy subjects was shown to be dependent on the rate of drug administration, providing a rational basis for the development of controlled release oral formulations [8].

Most clinically used dihydropyridines exhibit wide inter-individual variability in pharmacokinetics upon oral administration due to their extensive and variable presystemic elimination [2]. The within-subject variability in the pharmacokinetics of oral dihydropyridines is much less pronounced [15, 16]. With respect to the haemodynamic effects and concentration-effect relationships of dihydropyridines in normotensive subjects, wide inter-individual variability has been observed in most studies.

Except for nifedipine and lacidipine, all dihydropyridine calcium entry blockers currently approved for use in man are chiral compounds and have been clinically evaluated as racemic mixtures of two enantiomers. Most of the calcium entry blocking activity of *rac*-felodipine and *rac*-nitrendipine resides in their (S)-(–)-enantiomers [17–20], and stereoselectivity in their pharmacokinetics upon oral administration was recently demonstrated [19, 21, 22]. It is not known to what extent stereochemical factors contribute to the variability in the haemodynamic effects and clinical efficacy of dihydropyridine calcium entry blockers.

The aims of the present study were to assess and compare the haemodynamic effects of *rac*-felodipine, *rac*-nitrendipine and nifedipine in the same healthy subjects, and to characterise and compare the pharmacokinetic-pharmacodynamic relationships of these drugs, taking into consideration stereoselectivity in their metabolism.

* Pharmacokinetic data obtained in this study are reported in the accompanying paper

** *Present address:* Department of Clinical Pharmacokinetics, Glaxo Group Research Ltd., Greenford, Middlesex, UK

Materials and methods

Subjects and protocol

Twelve male subjects, mean (SD, range) age 25 y (5, 20–34 y) and mean weight 71 kg (7, 52–81 kg), healthy according to medical history, physical examination and routine laboratory analysis, participated after having given written informed consent. Three subjects were smokers. None of them used any concomitant medication.

The study protocol for this randomised, double-blind, three-way cross-over trial with washout periods of one week between treatments was approved by the Ethics Review Board of the Leiden University Hospital.

Subjects arrived by taxi at the clinical pharmacology unit at around 07.30 h, after an overnight fast and having refrained from all xanthine- and alcohol-containing beverages for at least 12 h.

After at least 30 min of rest (supine) followed by 30 min recording of baseline blood pressure and heart rate, the subjects received orally 20 mg of one of the experimental drugs, *rac*-felodipine, *rac*-nitrendipine and nifedipine as solutions (20 ml). All experiments started between 09.00 h and 09.15 h. Blood pressure and heart rate were measured noninvasively at 15 min intervals for 4 h after administration of the drugs, using a MPV-7201 oscillometric blood pressure monitor (Nihon Kohden, Amsterdam, The Netherlands). The mean of two successive measurements within one minute was used for further evaluation. Subjective adverse effects were assessed at 4, 9, 13, 23 and 33 h after administration, using 100-mm Visual Analogue Scales (VAS) referring to the possible adverse effects headache, flushing and palpitations.

The subjects remained supine until 4 h after administration, when a light lunch (sandwiches) was served. At 9 h after administration a normal dinner was served.

Blood samples were taken at regular intervals, always after measurement of blood pressure and heart rate, via an indwelling cannula up to 14 h, and thereafter by venepuncture, and plasma was obtained by centrifugation as soon as possible.

Analytical methods and protein binding

Plasma concentrations of nifedipine, *rac*-felodipine, *rac*-nitrendipine and of their enantiomers, were measured using HPLC, GC-ECD, and chiral-column HPLC with off-line GC-ECD detection. The protein binding of nifedipine, *rac*-nitrendipine and its enantiomers was measured using similar assay methodology as reported in the accompanying paper. For comparison of pharmacodynamic parameters of unbound drugs, an unbound fraction of 0.36% (0.08%) was assumed for the enantiomers of felodipine [23].

Evaluation of haemodynamic and adverse effects

Individual and mean profiles of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP, calculated as MAP = $^1/_3$ SBP + $^2/_3$ DBP) and heart rate (HR) were constructed. The maximum change from baseline of each parameter was determined and the area under these effect-time curves up to 4 h after administration ($AUE_{(0\rightarrow 4\,h)}$) was calculated by the linear trapezoidal method after correction for baseline values.

Self-scored adverse events were expressed as integers using a scale from 0 to 100, as measured on the VAS, and adverse event-time profiles were constructed.

Pharmacokinetic-pharmacodynamic modelling

Individual pharmacokinetic-pharmacodynamic relationships were assessed for HR and MAP up to 4 h after administration, during which period the subjects remained supine and abstained from food. It was explicitly assumed that no consistent change in HR and MAP would have occurred during the first 4 h if the subjects had been treated with placebo under similar conditions. In placebo-controlled experiments under comparable study conditions, we did not observed major changes in HR and MAP during a 4-h (morning) period in normotensive subjects on placebo treatment. Plasma concentrations of the drugs were estimated by linear interpolation at the times when haemodynamic parameters were measured but no blood sample had been taken.

For each individual with each treatment, HR and MAP were plotted against the plasma concentration of the drug, and the absence of hysteresis or proteresis was assessed by visual inspection. The measured haemodynamic parameters and corresponding plasma concentrations were fitted with equal weights for each data point to a sigmoidal E_{max}-model using Siphar® software (release 3.0, Simed, Creteil, France):

$$E = E_0 + \frac{E_{max} \cdot C^{\eta}}{EC_{50}^{\eta} + C^{\eta}} \qquad (1)$$

in which E, E_0 and E_{max} are the observed value, fitted pre-dose value and the maximum change in the haemodynamic parameter, respectively, C is the plasma concentrations, EC_{50} is the steady-state plasma concentration causing half of the maximal effect, and η is a power function that determines the shape of the concentration-effect relationship [13]. The maximum effect was expressed in the original units (E_{max}), and also as percentage change from E_0 (%E_{max}). In addition, the plasma concentration associated with a 10% change in the haemodynamic parameter ($C_{10\%}$) was estimated. EC_{50} and $C_{10\%}$ were also calculated for unbound drug (EC_{u50} and $C_{u10\%}$), using each individual's own free fractions of the compounds involved, except for felodipine, for which historical protein binding data were used [23].

Alternative E_{max}- and log-linear pharmacokinetic-pharmacodynamic models were evaluated as well, but almost always the sigmoidal E_{max}-model performed best as judged by the residual sum of squares, standard error of parameter estimates and the Akaike Information Criteria.

Statistical analysis

The haemodynamic parameters $AUE_{(0\rightarrow 4\,h)}$ and maximum change from baseline are reported as mean (SD). The distributions of most parameters obtained by fitting the data to a sigmoidal E_{max}-model

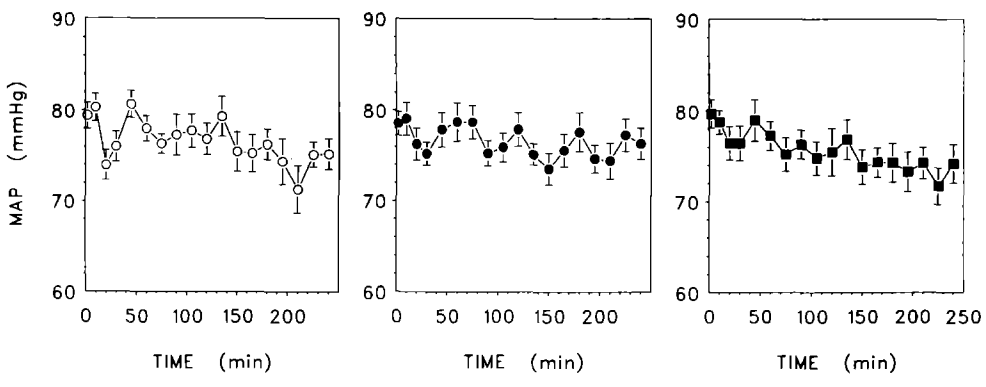

Fig. 1. Mean arterial pressure (MAP) after oral administration (20 mg solution) of *rac*-felodipine (○) *(left)*, *rac*-nitrendipine (●) *(middle)* and nifedipine (■) *(right)* to normotensive subjects (mean with sem, $n = 12$)

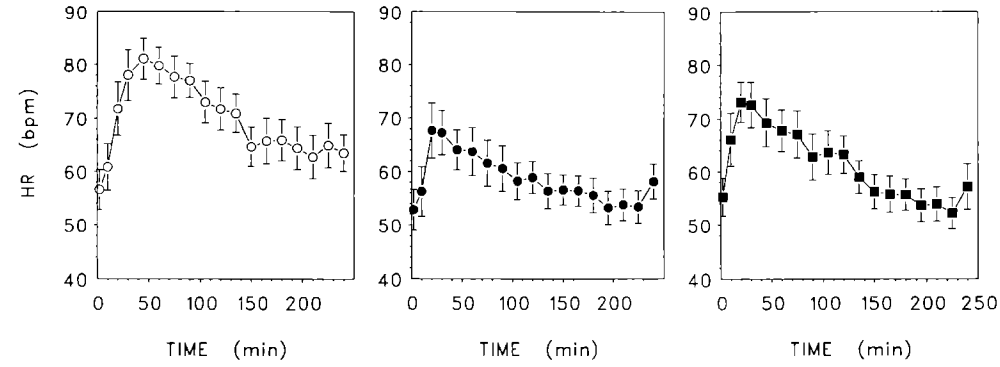

Fig. 2. Heart rate (HR) after oral administration (20 mg solution) of *rac*-felodipine (○) *(left)*, *rac*-nitrendipine (●) *(middle)* and nifedipine (■) *(right)* to normotensive subjects (mean with sem, $n = 12$)

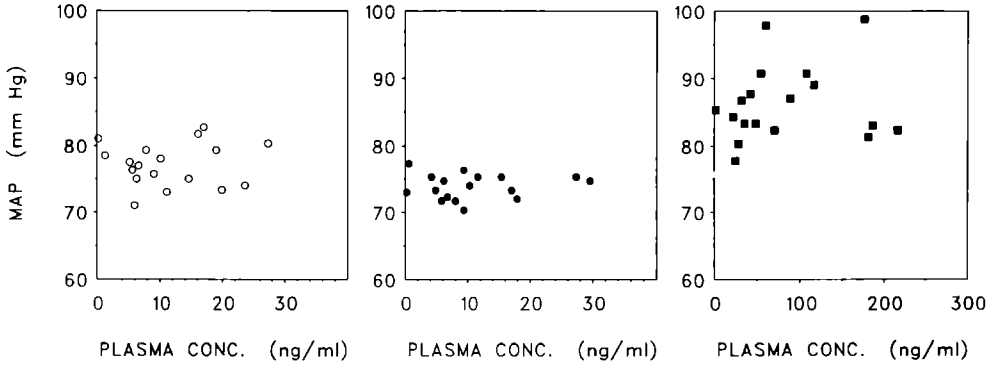

Fig. 3. Example of individual relationships between changes in mean arterial pressure (MAP) and plasma concentration of *rac*-felodipine (○) *(left)*, *rac*-nitrendipine (●) *(middle)* and nifedipine (■) *(right)*

were clearly skewed, so these results are reported as geometric mean {95% confidence interval}. Comparison of haemodynamic parameters between treatments was performed with two-way Analysis of Variance (ANOVA), followed by two-tailed paired t-tests if the overall significance level of $\alpha = 0.05$ was reached. In order to assess relative differences between these parameters, the data were transformed to logarithms prior to these pair-wise comparisons. $AUE_{(0\to4\,h)}$ was also tested against zero using t-tests on untransformed data. Self-scored adverse effects were compared with repeated-measures ANOVA, evaluating the treatment effect and treatment × time interaction. Product-moment coefficients of correlation (r) between parameters were calculated and tested against zero using the two-tailed t-distribution at as significance level of $\alpha = 0.05$.

Results

Haemodynamic parameters

Mean profiles of MAP and HR *versus* time are shown in Figs. 1 and 2. The shapes of the profiles of SBP and DBP (not shown) were very much like that of MAP. Relatively small (7–13%) maximum decreases from baseline values were observed in mean SBP, DBP and MAP, whereas mean HR was increased up to a maximum of 47% above the baseline value by *rac*-felodipine, 40% by *rac*-nitrendipine and 38% by nifedipine. The maximum changes in SBP, DBP and MAP were not statistically evaluated because of the small changes in the parameters and their wide variability at the times at which the largest decrease in blood pressure was measured (20–240 min). Baseline values (overall mean, $n = 36$) of SBP was 117 (9) mm Hg, of DBP 62 (4) mm Hg and of HR 55 (13) bpm, and were not different between treatments (all $P > 0.3$). The $AUE_{(0\to4h)}$ for these parameters differed from zero with all treatments (Table 1).

The baseline corrected $AUE_{(0\to4\,h)}$ after *rac*-felodipine treatment was 197% {74–204%} and 180% {70–362%} larger than that after treatment with nifedipine and *rac*-nitrendipine, respectively (both $P < 0.001$). The mean maximum change in HR from baseline after *rac*-felodipine treatment was 26% {11–43%} ($P = 0.002$) and 29% {0–69%} ($P = 0.05$) higher than after nifedipine and *rac*-nitrendipine treatment, respectively. There were no significant differences between treatments in baseline corrected $AUE_{(0\to4\,h)}$ for SBP, DBP and MAP (all $P > 0.1$).

Pharmacokinetic-pharmacodynamic relationships

No consistent hysteresis was observed when plotting MAP and HR against plasma concentrations. Examples of concentration-effect relationships for MAP and HR, all

Table 1. Baseline-corrected areas under effect-time curves up to 4 h after administration ($AUE_{(0\to4\,h)}$) and maximum changes in heart rate (*max* HR) after oral administration of 20 mg (solution) of nifedipine, *rac*-Felodipine and *rac*-Nitrendipine. (mean with (SD) and [range], $n = 12$)

	$AUE_{(0\to4\,h)}$ SBP mm Hg·h	$AUE_{(0\to4\,h)}$ DBP mm Hg·h	$AUE_{(0\to4\,h)}$ HR beats·min^{-1}·h	*max* HR beats·min^{-1}
Nifedipine	−31 (29)** [−78–1]	−16 (14)** [−41–6]	24 (16)*** [5–46]	21 (4)[a] [14–29]
rac-Felodipine	−15 (20)* [−47–14]	−16 (8)*** [−32–2]	54 (21)*** [12–86]	27 (8)[a] [13–40]
rac-Nitrendipine	−17 (25)* [−66–15]	−10 (8)** [−25–1]	22 (14)*** [2–54]	21 (6)[a] [7–32]

t-test comparison with zero: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; [a] not tested

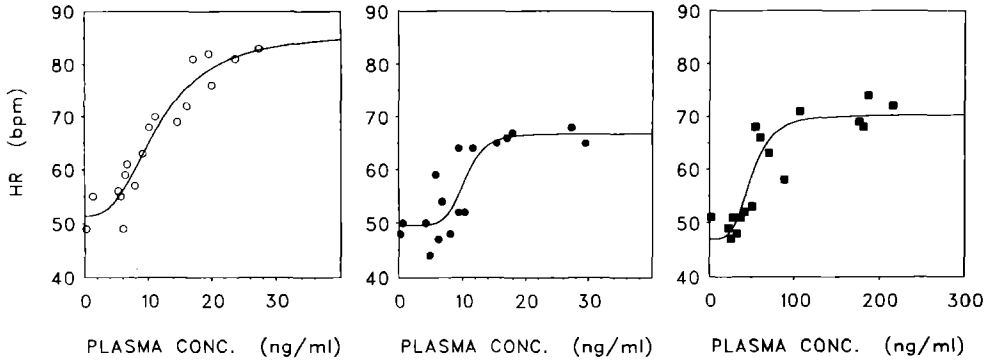

Fig. 4. Example of individual relationship between changes in heart rate (HR) and plasma concentration of *rac*-felodipine (○) *(left)*, *rac*-nitrendipine (●) *(middle)* and nifedipine (■) *(right)*. Solid lines fitted to a sigmoidal E_{max}-model

Table 2. Pharmacodynamic parameters for the effects on heart rate, fitted to a sigmoidal E_{max}-model (geometric mean with {95% confidence interval}, $n = 12$)

	Nifedipine	*rac*-Felodipine	*rac*-Nitrendipine	(S)-felodipine	(S)-nitrendipine
E_0 beats · min^{-1}	52.9 {45.9–60.9}	56.8 {49.6–65.0}	52.4 {46.4–59.2}	56.6 {49.4–64.9}	52.5 {46.4–59.2}
E_{max} beats · min^{-1}	21.3 {16.1–28.2}	24.3 {20.0–29.6}	21.8 {15.9–29.9}	25.1 {20.3–30.9}	21.5 {15.8–29.4}
$\%E_{max}$ (%)	40.2 {27.2–58.5}	42.8 {32.8–55.9}	41.6 {29.4–59.0}	44.3 {33.4–58.7}	41.0 {29.1–57.8}
EC_{50} (ng · ml^{-1})	92.3 {66.8–128}	10.8 {6.5–18.0}	16.8 {6.3–45.0}	7.5 {4.4–12.8}	12.2 {5.3–27.9}
EC_{u50} (pg · ml^{-1})	1509 {1075–2116}	39 {23–65}	238 {101–562}	27 {16–46}	183 {89–375}
$C_{10\%}$ (ng · ml^{-1})	54.3 {37.2–79.1}	7.0 {3.9–12.3}	9.4 {3.3–26.7}	4.8 {2.7–8.3}	7.6 {3.8–15.0}
$C_{u10\%}$ (pg · ml^{-1})	887 {614–1280}	25 {14–44}	133 {54–328}	17 {10–31}	114 {65–200}
η	3.9 {2.2–7.0}	3.4 {2.3–5.1}	3.4 {1.9–5.9}	3.5 {2.4–5.2}	3.8 {2.3–6.3}

Symbols: see *Methods:* pharmacokinetic-pharmacodynamic modelling

in the same individual, are shown in Figs. 3 and 4. Good ($r \geq 0.9$) or reasonable ($0.7 \geq r > 0.9$) relationships were obtained in 48% and 44% of the cases, respectively, when fitting HR and plasma concentrations to the sigmoidal E_{max}-model (all $r > 0.6$). The mean r varied from 0.81 (*rac*-nitrendipine) to 0.90 ((S)-felodipine). There was considerable interindividual variability in the estimates of EC_{50} and E_{max}, in particular for *rac*-nitrendipine and (S)-nitrendipine (Table 2).

No differences between treatments were observed in E_0, E_{max} and η, and on average E_{max} was 42% of the corresponding E_0. However, large differences between compounds were observed in EC_{50}, EC_{u50}, $C_{10\%}$ and $C_{u10\%}$ (Table 2). With HR as the haemodynamic variable, the EC_{u50} of nifedipine was 6.3 {3.1–13.0}-times higher than that of *rac*-nitrendipine, which itself was 6.1 {3.4–11.0}-times higher than the EC_{u50} of *rac*-felodipine. Results for $C_{u10\%}$ were quite comparable (Table 2). However, no significant differences in EC_{50} and $C_{10\%}$ were observed between *rac*-felodipine and *rac*-nitrendipine based upon total plasma concentrations ($P > 0.2$).

In contrast to HR, poor ($r < 0.6$) results were obtained in more than 70% of the cases when fitting MAP and plasma concentrations to the sigmoidal E_{max}-model. The mean r varied from 0.43 (*rac*-nitrendipine) to 0.51 (nifedipine). Furthermore, in almost 40% of cases a positive E_{max} was obtained, i.e. an increase in blood pressure, and in many cases unrealistic values for E_{max}, EC_{50} and η were obtained. These results for MAP were therefore not statistically analysed or reported.

Correlations between pharmacodynamic parameters

Correlations between treatments for baseline-corrected $AUE_{(0\to4\,h)}$ of HR and for the maximum change in HR were modest ($0.31 < r < 0.77$) and only borderline significance was reached on some occasions ($0.02 < P < 0.3$). Without baseline correction there were highly significant correlations ($0.76 < r < 0.90$) between treatments for $AUE_{(0\to4\,h)}$ of HR and for the maximum HR, mainly due to the high correlation between baseline HR within individuals ($0.75 < r < 0.88$; all $P < 0.001$). All correlation coefficient between treatments for baseline corrected $AUE_{(0\to4\,h)}$ of SBP, DBP and MAP were low and were not significantly different from zero ($0.04 < r < 0.51$; $P > 0.08$).

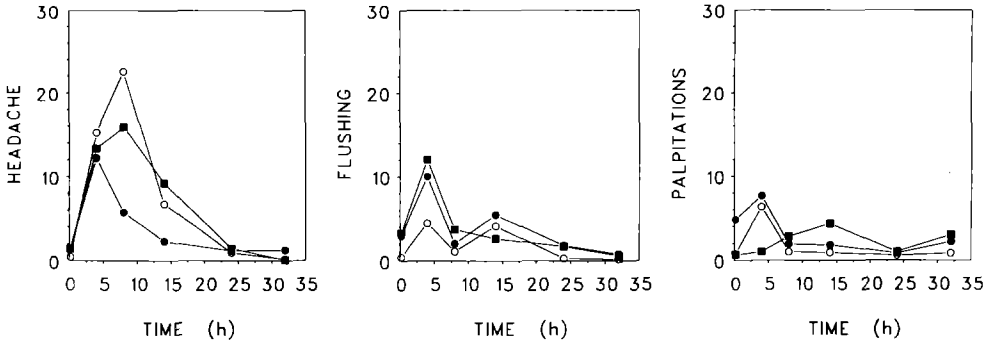

Fig. 5. Mean scores ($n = 12$) of headache *(left)*, flushing *(middle)* and palpitations *(right)* with *rac*-felodipine (○), *rac*-nitrendipine (●) and nifedipine (■) treatment

There were significant correlations between treatments for the fitted E_0 and EC_{50} for the effects on HR ($0.65 < r < 0.79$; $P < 0.03$). E_{max}, $C_{10\%}$ and η were not significantly related between treatments ($r < 0.47$; $P > 0.1$).

Adverse events

One subject (nifedipine treatment) experienced dizziness upon leaving his bed just prior to lunch and subsequently fainted. He recovered completely within a few minutes and was able to complete the study, as did all other subjects. Two subjects complained of moderate headache, one on nifedipine and one on felodipine, which was treated at the subjects' request with paracetamol (500 mg orally) after the 8-h measurements. The self-scored adverse events (Fig. 5) were therefore only analysed up to 8 h after drug administration. There was no significant difference between treatments in any of the three self-scored adverse events (all $P > 0.1$).

Discussion

Haemodynamic effects

A marked increase in heart rate from baseline-value was observed after all three treatments. The equal dosages administered are not equipotent: heart rate was significantly higher after *rac*-felodipine than after nifedipine and *rac*-nitrendipine. The baseline corrected $AUE_{(0\to4\,h)}$ for HR after *rac*-felodipine treatment was almost 3-times higher than after nifedipine and *rac*-nitrendipine. Blood pressure (SBP, DBP, MAP) changed much less and inconsistently in these normotensive subjects, and did not differ between treatments. Although the $AUE_{(0\to4\,h)}$ for blood pressure after all treatments was significantly different from zero (Table 1), it is difficult to conclude that the test drugs lowered blood pressure in normotensive subjects because no placebo treatment was included in the study.

Pharmacokinetic-pharmacodynamic relationships

Mean arterial pressure could not be satisfactorily fitted to a sigmoidal E_{max}-model, and parameter estimates were unreliable and often unrealistic. Even when applying a linear pharmacodynamic model, significant individual relationships between concentration and change in MAP were found in only 25% of the cases, equally distributed over compounds (data not shown). Half of these relationships had a positive slope and the mean slope was not different from zero for any compound (all $P > 0.7$). Also with mean and pooled data, there was no significant relationship between plasma concentration and MAP. Similar results were obtained with SBP and DBP (data not shown), so we conclude that the small changes in blood pressure from baseline in normotensive subjects were not related to the plasma concentrations of the drugs under investigation.

Because of the profound effects of the oral solutions on heart rate, the latter could generally be fitted to plasma concentrations using a sigmoidal E_{max} model without consistent signs of hysteresis. Generally, E_0 was fitted as parameter of the model, but in a few cases it was necessary to fix the no-drug effect to the measured pre-treatment value in order to obtain realistic parameter estimates. In a few instances the estimated E_{max} was outside the range of observations, producing less reliable estimates of E_{max} and EC_{50}. The predicted concentration associated with a 10% change in heart rate ($C_{10\%}$) was also calculated, as it is much less influenced by estimates of E_{max}. The relative $C_{10\%}$ values of all the compounds were quite similar to the relative values of EC_{50}.

Based on total plasma concentrations, and corrected for the differences in molecular weight, the potencies of *rac*-nitrendipine and *rac*-felodipine for their indirect effects on heart rate in normotensive subjects were not significantly different. They were about 4- and 13-times more potent than nifedipine. Based upon unbound plasma concentrations (EC_{u50}), and corrected for the differences in molecular weight, the average relative potencies for the effect on heart rate were approximately: nifedipine = 1, *rac*-nitrendipine = 7, (S)-nitrendipine = 9, *rac*-felodipine = 43 and (S)-felodipine = 60. For this calculation published protein binding data for felodipine were used [23], and a lack of stereoselectivity in the protein binding of the felodipine enantiomers was assumed. These relative potencies compare reasonably well with *in vitro* receptor binding affinities and *ex vivo* pharmacodynamic effects [1, 18, 24–27].

The cardiovascular activity of both *rac*-nitrendipine and *rac*-felodipine resides predominantly in their (S)-(−)-enantiomers, which were shown to be at least 7–13-times as potent as their corresponding (R)-enantiomers in spontaneous hypertensive rats [18], and an 8–20-fold difference in *in vitro* binding affinity of the enantiomers has

been reported [17, 18]. Furthermore, oral administration of 80 mg (R)-nitrendipine did not cause any haemodynamic effects in man [20]. Because of these findings it was assumed here that the (R)-enantiomers of felodipine and nitrendipine did not significantly contribute to the observed haemodynamic effects, thus allowing estimation of the pharmacodynamic parameters of the (S)-enantiomers without administering them separately.

For other chiral dihydropyridines studied in this respect, marked differences in pharmacodynamic parameters between enantiomers have been observed [1, 17, 18, 28–32], even including opposed effects in some cases [26, 33]. Pharmacodynamic differences between enantiomers of the dihydropyridines generally appear to be much larger than their pharmacokinetic differences [19, 21, 22, 31, 34]. The pharmacokinetic parameters calculated for the (S)-enantiomers of felodipine and nitrendipine are not necessarily identical to the values that might have been obtained had the pure (S)-enantiomers been administered. Pharmacodynamic interactions at receptor binding sites and mutual effects on homeostatic feed-back mechanisms cannot be excluded.

Comparison with published reports

A significant relationship between the plasma concentration and the haemodynamic effect in normotensive subjects, especially for reflex tachycardia, has been reported for nifedipine [3–9], *rac*-felodipine [10] and *rac*-nitrendipine [5, 11], as well as for other chiral dihydropyridines. Several of these relationships were based on pooled data sets, which did not allow assessment and appreciation of inter-individual variability. In addition, most have used (log-) linear pharmacodynamic models, which, by definition, are not able to predict a maximum effect, despite the fact that the biological responses to receptor-mediated drug actions must reach a maximum if the concentration is allowed to increase over a large range [13]. Only a limited number of authors was able to model pharmacokinetic-pharmacodynamic data obtained from normotensive healthy subjects with a (sigmoidal) E_{max} model [5–7, 35]. Two of the reports were based on modelling of mean values, which may result in biassed parameter estimates. In hypertensive patients a more pronounced response on blood pressure is generally observed, allowing easier modelling of the effects on blood pressure with a linear [36–40] or (sigmoidal) E_{max}- [6, 41–46] model than in normotensive subjects.

The EC_{50} of nifedipine for its effect on heart rate was more than twice as large as published EC_{50}-values for various haemodynamic effects in normotensive and hypertensive subjects (overall mean 39 $ng \cdot ml^{-1}$; range of mean values 19–78 $ng \cdot ml^{-1}$), but the observed $\%E_{max}$ values were quite comparable [5–7, 35, 41]. For *rac*-felodipine a four-fold larger EC_{50} for HR was observed here compared to published values for the effect on blood pressure in hypertensive patients (mean 2.7 $ng \cdot ml^{-1}$; range of mean values 1.8–3.5 $ng \cdot ml^{-1}$) [42–44, 46]. No EC_{50} of *rac*-felodipine in normotensive subjects appears to have been published. The reasons for these discrepancies are unclear at present. The EC_{50}, E_{max} and η of *rac*-nitrendipine compares very well with published data for effects on heart rate in healthy subjects, although obtained by fitting mean data [5].

The EC_{50} for the effects on blood pressure, a clinically more relevant haemodynamic variable, may very well be different from that for the effects on heart rate, but the few studies which have modeled both HR and DBP did not show a major difference [6, 7, 45]. In addition, all parameter estimates may be different in (elderly) hypertensive patients than in these young normotensive healthy subjects, and may also be influenced by dosage form [35], and the rate of drug administration [8]. Because of the occurrence of stereoselective pharmacokinetics of felodipine and nitrendipine after oral administration but not by the *i.v.* route [22], differences in parameter estimates for the racemic drugs are to be expected when comparing data after intravenous and oral administration.

Correlations between the effects of the dihydropyridines

Only correlations between the parameters of nifedipine, *rac*-felodipine and *rac*-nitrendipine were evaluated. By definition, the small variability in stereoselectivity of their pharmacokinetics [21, 22] will result in a high correlation between the parameters of racemic drugs and their enantiomers upon administration of the racemate. This small variability also prevents confirmation that the (S)-enantiomers indeed are the active enantiomers in man *in vivo* on the basis of the data obtained in the present study. Administration of separate enantiomers would be necessary for this purpose, which might be difficult to justify without appropriate pre-clinical safety evaluation.

The estimated EC_{50}-values were significantly correlated between treatments, as were E_0 and measured baseline heart rates. Other pharmacodynamic parameters (E_{max}, η, and baseline-corrected $AUE_{(0\rightarrow 4\,h)}$) were poorly correlated between treatments. Despite many similarities in the molecular pharmacological characteristics of these dihydropyridines [1, 33], it must be recognized that their ultimate *in vivo* haemodynamic effects are brought about through much more complex regulatory mechanisms.

In conclusion, *rac*-felodipine had the most pronounced effect on heart rate. Changes in blood pressure were small and did not differ between the treatments. However, normotensive subjects are not the most appropriate model in which to investigate and compare the effects of dihydropyridines on blood pressure, because these subjects have efficient homeostatic mechanisms that keep the blood pressure within a narrow range. Hypertensive patients are likely to be a better model for investigation and comparison of the effects of dihydropyridine on blood pressure.

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Prof. Dr. D. D. Breimer
Center for Bio-Pharmaceutical Sciences
Division of Pharmacology
P. O. Box 9503
2300 RA Leiden
The Netherlands