Pharmacokinetics and Pharmacodynamics of the Enantiomers of Gallopamil

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Accepted for publication February 7, 1997

ABSTRACT

The pharmacokinetics and pharmacodynamics of the enantiomers of the calcium antagonist gallopamil have been investigated in six healthy volunteers. Each subject was studied on five occasions after receiving, in randomized order: placebo, 25 mg of (R)-gallopamil, 25 mg of (S)-gallopamil, 50 mg of pseudoracemic [25 mg of deuterated (S)-gallopamil and 25 mg of (R)-gallopamil] and 100 mg of (R)-gallopamil HCl orally. After separate administration, the apparent oral clearances of both enantiomers were similar [(R), 15.1 ± 9.9 liters/min; (S), 11.0 ± 6.0 liters/min], indicating that gallopamil first-pass metabolism is not stereoselective. After coadministration, the apparent oral clearance of each enantiomers decreased [(R), 5.9 ± 2.8 liters/min; (S), 5.8 ± 2.66 liters/min], suggesting that a partial saturation of first-pass metabolism occurs because the dose was twice as high than for the single enantiomers. Serum protein binding and renal elimination of gallopamil are stereoselective, favoring (S)-gallopamil. Analysis of urine samples revealed a marked degree of stereoselectivity in the formation of O- and N-dealkyl metabolites. Because these showed opposite stereoselectivity, canceling out each other, the net result was no or only marginal stereoselectivity. Twenty-five milligrams of (S)-gallopamil prolonged the PR interval in all subjects; however, a greater effect was elicited by 50 mg of (RS)-gallopamil. (R)-Gallopamil (100 mg) did not significantly alter the PR interval, although higher concentrations were attained than after the pseudoracemate. Based on a consideration of (S)-gallopamil serum concentrations, a comparable relationship between (S)-gallopamil level and effect occurred after (S)- and (RS)-gallopamil, indicating that the pharmacological effect produced by the racemate could be totally accounted for by the higher concentrations of (S)-gallopamil attained.

Gallopamil [2-(3,4,5-trimethoxyphenyl)-2-isopropyl-5-[(3,4-dimethoxyphenethyl) methyl-amino]valeronitrile] (D 600) (fig. 1) is a calcium antagonist with phenylalkylamine structure used in the treatment of angina pectoris (Brogden and Benfield, 1990). It is a methoxy derivative of verapamil, and the small change in structure results in a 10-fold increase in potency in terms of vasodilation, negative inotropic action and the spectrum of effects elicited (Eichelbaum and Gross, 1996), and it is important to establish the contribution of the individual enantiomers of racemic drugs to the desired and undesired pharmacological effects of the racemate. In vitro studies have shown that (S)-gallopamil is a more potent negative inotropic agent and vasodilator than (R)-gallopamil (Bayer et al., 1975; Müller and Wilsmann, 1982; Nawrath and Raschack, 1987; van Amsterdam et al., 1990). (S)-Verapamil is also a more potent negative dromotropic agent in vitro than (R)-verapamil and this difference in relative potency has also been observed in man in vivo (Echizen et al., 1985a, 1985b). As yet, however, no data on the relative potencies of the enantiomers of gallopamil in humans have been published.

Differences in the absorption, metabolism, protein binding and urinary excretion of the enantiomers of racemic drugs occur (Eichelbaum and Gross, 1996). It is well established that the pharmacokinetics of racemic verapamil are stereoselective (Eichelbaum et al., 1984; Vogelgesang et al., 1984) as

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\textbf{ABBREVIATIONS:} C_{\text{max}}, maximum serum concentration; t_{\text{max}}, time at which C_{\text{max}} occurs; \lambda, terminal elimination rate constant; t_{1/2}, terminal elimination half-life; AUC, area under the serum concentration-time curve; MRT, mean residence time; f_u, free fraction; CL_{ap}, apparent oral clearance; CL_{cr}, renal clearance; A_{ex}, amount excreted unchanged in urine; F, bioavailability; B/P, ratio of whole blood to serum gallopamil concentrations; E_{\text{max}}, maximum effect; E_{D2}, serum gallopamil concentration eliciting 50% of E_{\text{max}}. N, parameter affecting the slope of the concentration-effect curve; C_{\text{cr}}, serum gallopamil concentration at \(n\) hours after drug administration; ER, extraction ratio; AV, atrioventricular; GC-MS, gas chromatography-mass spectroscopy.
metabolism, the major pathway of elimination, favors the (S)-enantiomer. By analogy with verapamil, gallopamil is eliminated principally by metabolism (Stieren et al., 1983; Weymann et al., 1989). In the rat and humans, both O- and N-dealkylated metabolites have been identified in the urine and in the bile as sulfate and glucuronide conjugates (Mutlib and Nelson, 1990a, 1990b; Weymann et al., 1989). The similarity in structure and disposition of gallopamil and verapamil suggests that the metabolism and, consequently, disposition of gallopamil may be stereoselective. However, to date only the disposition of racemic gallopamil has been reported (Eichelbaum, 1989; Stieren et al., 1983), and the pharmacokinetics of the individual enantiomers of gallopamil have not been described.

Gallopamil improves the ratio of myocardial oxygen demand to supply (De Servi et al., 1987). The influence of racemic gallopamil on blood pressure, heart rate and exercise stress test electrocardiography has been reported in normotensive subjects (Hopf et al., 1984; Khurmi et al., 1984; Rettig et al., 1983); however, in these studies, the relationship between the pharmacological response and gallopamil serum concentrations has not been investigated. Furthermore, the influence of gallopamil on peripheral blood flow, peripheral vascular resistance and plasma renin concentrations has not been reported. The contribution of the individual enantiomers of gallopamil to the pharmacological effects observed in humans has not been examined.

We performed this study to investigate (1) whether the pharmacokinetics of (R)- and (S)-gallopamil differ, (2) which pathways of metabolism are stereoselective on the basis of analysis of the urinary excretion of the major metabolites of gallopamil and (3) the relative effects of (R)- and (S)-gallopamil on cardiovascular and electrocardiographic parameters, peripheral blood flow and plasma renin concentrations.

The disposition and pharmacological effects of single oral 25-mg doses of (R)- and (S)-gallopamil after separate and simultaneous administration were compared in healthy volunteers using a randomized, placebo-controlled study design. (R)-Gallopamil is less potent than (S)-gallopamil, as demonstrated in vitro (Bayer et al., 1975); therefore, an additional 100-mg dose of (R)-gallopamil was also investigated. A pseudoracemate, in which (S)-gallopamil is labeled with two deuterium atoms (fig. 1) and (R)-gallopamil is unlabeled, was used for simultaneous enantiomer administration to measure the concentrations of the stereoisomers (Brown, 1990; Eichelbaum et al., 1982).

**Methods**

**Materials.** Hard-gelatin capsules containing placebo, 25 mg of (–)-(S)-gallopamil HCl, 25 mg of (+)-(R)-gallopamil HCl and 25 mg of [²H₂]-(–)-(S)-gallopamil HCl were used that were >99% isotopically and optically pure. The enantiomeric composition of the gallopamil capsules was also investigated using a stereospecific high-perfor-
mance liquid chromatography technique based on a method developed for 1,4-dihydropyridine calcium antagonists (Fischer et al., 1993). Base-line resolution of the enantiomers of gallopamil was achieved using a Chiralpak AD column (Daicel Chemical Industries Ltd., Tokyo, Japan) maintained at 40°C with a mobile phase of hexane/2-propanol (95:5) containing 0.2% diethylamine pumped at a flow rate of 1 ml/min. Appropriate fractions eluting from the column at the retention times of (S)- and (R)-gallopamil (13.04 and 16.5 min, respectively) were collected and assayed for gallopamil by GC-MS. The (S)-gallopamil capsules contained 0.11% (R)-gallopamil, and the (R)-gallopamil capsules contained 0.14% (S)-gallopamil. [2H2](-)-(S)-Gallopamil HCl, labeled with two deuterium atoms at C5, was used when the enantiomers were coadministered (fig. 1). In an initial study, 25 mg of (S)-gallopamil HCl and 25 mg of [2H2]-(S)-gallopamil HCl were administered to one healthy volunteer. The serum concentration-time profiles of [2H2]-(S)- and [2H2]-(−)-(S)-gallopamil were superimposable, and therefore a significant isotope effect can be excluded.

The following metabolites of gallopamil were available as reference substances (fig. 1): D832-HCl [2-methyl-3-cyano-3-(3,4,5-trimethoxy-phenyl)-7-azaa-octane hydrochloride], D829-HCl [1-(3,4,4,5-trimethoxy-phenyl)-3-methylaza-7-cyano-7-(3,5-dimethoxy-4-hydroxyphenyl)-7-methylaza-9-(3-hydroxy-4-methoxyphenyl)-nonane hydrochloride], D845-HCl [1-(3-methoxy-4-hydroxyphenyl)-3-methylaza-7-cyano-7-(3,4,5-trimethoxyphenyl)-8-methyl-nonane hydrochloride], D829-HCl [1-(3,4-dimethoxyphenyl)-3-aza-7-cyano-7-(3,5,4-trimethoxyphenyl)-8-methyl-nonane hydrochloride], D832-HCl [2-methyl-3-cyano-3-(3,4,5-trimethoxy-phenyl)-7-azaa-octane hydrochloride], and D845-HCl [1-(3-methoxy-4-hydroxyphenyl)-3-methylaza-7-cyano-7-(3,4,5-trimethoxyphenyl)-8-methyl-nonane hydrochloride].

Subjects. Six healthy male volunteers participated in the study after a thorough physical examination was performed and written informed consent had been obtained. Their age ranged from 24 to 36 years, and their weight ranged from 63 to 86 kg. All volunteers were cigarette smokers and abstained from smoking for 12 hr before each dose until the last blood sample was taken.

Protocol. This study was approved by the Ethics Committee of the Robert-Bosch-Hospital (Stuttgart, Germany). All gallopamil doses were administered under medical supervision. Each subject was studied on five occasions with a 7- to 14-day interval between study days. In randomized order, each subject was administered (1) placebo, (2) 25 mg of (R)-gallopamil HCl (47.98 μmol), (3) 25 mg of (S)-gallopamil HCl (47.98 μmol), (4) 25 mg of (R)-gallopamil HCl and 25 mg of [2H2]-(S)-gallopamil HCl (47.98 μmol of each enantiomer/pseudoracemate (S)-gallopamil and (5) 100 mg of (R)-gallopamil HCl (191.9 μmol).

The capsules were administered with 100 ml of mineral water after an overnight fast. A standard breakfast was administered 3 hr after capsule administration. The volunteers were recumbent from 30 min before drug administration to ≤5 hr postdose while pharmacodynamic effects were monitored. Blood samples (8 ml) were withdrawn through an indwelling cannula in a forearm vein before gallopamil administration; and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2.5, 3, 4, 5, 8, 9, 11, 12, 14 and 15 hr; and via venipuncture at 24 and 25 hr postdose. One-milliliter aliquots of whole blood were transferred to chilled tubes containing EDTA and immediately centrifuged, and plasma for analysis of renin concentrations was stored at −20°C. The remaining blood sample, which was transferred to a glass tube, was kept at room temperature for 30 min and then centrifuged at 1500 × g for 15 min. Serum samples were stored in glass tubes at −20°C until assayed. An additional whole blood sample for determination of blood to serum concentration ratio was taken from each subject two hr after drug administration and stored at −20°C. The urine excreted from 0 to 24 hr and 24 to 48 hr post-dose was collected, the volume determined and a 50 ml aliquot of each sample stored at −20°C until assayed.

Pharmacodynamic measurements. Pharmacodynamic effects were assessed in each subject before capsule administration and at the time of blood sampling for 5 hr postdose. Blood pressure (systolic, diastolic and mean arterial pressure) and heart rate were measured using an automated sphygmomanometer (Dinamap 1846 SX, Critikon GmbH, Norderstedt, Germany). Electrocardiographic intervals [P wave, PR interval, QRS interval, QT and corrected QT (QTc) intervals] were measured with an electrocardiograph (CS 6/12, Schiller, Baar, Switzerland). Ten measurements were taken at each time point, and the data were transferred, stored and processed with the use of dedicated software. Peripheral blood flow in both legs was determined at the time of each blood sampling using an automatic venous occlusion plethysmograph (Infraton Vassokrift, Boucke, Tübingen, Germany), and the mean value of 10 measurements is reported. The peripheral vascular resistance was calculated by dividing the mean arterial blood pressure by leg blood flow.

Analytical techniques. Gallopamil and [2H2]gallopamil were measured in serum using a specific GC-MS technique with selected ion monitoring (Gross et al., 1990). The method is very sensitive and has a limit of quantification of 0.192 nM = 1 ng/ml (within-day reproducibility, 4.8%, n = 9; between-day reproducibility, 12.3%, n = 47). This technique was used without modification and with comparable accuracy and reproducibility to determine the concentration of gallopamil and [2H2]gallopamil in urine and whole blood.

The serum concentrations of (R)- and (S)-gallopamil after the 100-mg dose of (R)-gallopamil were measured in the serum sample at tmax from each subject (see table 3) to assess any chiral inversion. Gallopamil was extracted from serum, and the enantiomers were resolved using the chiral high-performance liquid chromatography technique described above. Appropriate column fractions containing the separated enantiomers were collected and assayed for gallopamil by GC-MS (Gross et al., 1990).

Gallopamil metabolites in aliquots of the 0- to 48-hr urine samples collected after the single 50-mg dose of pseudoracemic gallopamil were assayed by GC-MS. Because the metabolites retained C5 of the gallopamil molecule and, consequently, the deuterium label, the enantiomers of the metabolites could be individually identified on the basis of the differences in the mass fragments monitored. After hydrolysis and liquid-liquid extraction, the samples were analyzed by GC-MS. In brief, to 2 ml of urine we added 440 μl of 4 M aqueous sodium acetate solution, pH 5, the internal standards and 60 μl of β-glucuronidase/arylsulfatase (Helix pomatia, 5.5/2.6 units/ml, Boehringer-Mannheim Biochemica, Mannheim, Germany). Hydrolysis was stopped after 24 hr at 37°C by refrigeration. After alkalization of 1 ml of the hydrolyzed sample with 400 μl of 10% sodium carbonate, 5 ml of diethylether/hexane (50:50 v/v) was added, and the tubes were mixed for 10 min and centrifuged at 4000 rpm for 10 min. The organic phase was transferred to tapered evaporation tubes and evaporated. Acetic acid anhydride (35 μl) and 5% triethylamine in acetonitrile (45 μl) were added to the residue. After being heated for 45 min at 50°C, the derivatization reagent was evaporated under nitrogen. The residue was reconstituted in 40 μl of acetonitrile, and an aliquot (2 μl) was assayed by electron impact selected-ion-monitoring GC-MS using a modification of the temperature program used for gallopamil (Gross et al., 1990). The retention times of the metabolites were D845 25.3 min, PR53 19.1 min, SZ488 18.1 min, D829 18.9 min and D832 9.4 min. Plasma renin concentrations were determined by immunoradiometric assay (Renin IRMA Pasteur, ERIA Diagnostics Pasteur, Marves la Coquette, France).

The serum protein binding of the enantiomers of gallopamil was determined by equilibrium dialysis at 37°C (Dianorm Equilibrium Dialyzer, Spectrum Instrument Co., Houston, TX). One-milliliter serum samples taken 2 hr after gallopamil administration were dialyzed for 2 hr across a SpectraPor 2 dialysis membrane against 1 ml of pH 7.4 Sorensen’s buffer. Because gallopamil binding is sensitive to pH (Rutledge and Szlacky, 1988), the pH of all serum samples was adjusted to pH 7.2 to ensure a pH of 7.4 at the end of dialysis. The fs of gallopamil was corrected for volume shifts during dialysis by measuring changes in protein concentration during dialysis (Lima et al., 1983). The technique was reproducible (fraction bound =
Data treatment and statistical analysis. Standard equations were used to calculate model-independent pharmacokinetic parameters (Rowland and Tozer, 1989). C\text{max} and t\text{max} were established from the measured serum concentration-time data. The λ was determined by least-squares regression of the terminal linear portion of the log serum concentration-time profile, and terminal half-life, t\text{1/2}, was calculated as 0.693/λ. AUC\text{(0–25 hr)} was calculated using the linear trapezoidal rule and extrapolated to infinity by the addition of C\text{∞}/λ. CL\text{w} was calculated as dose/AUC. MRT was calculated as the area under the first moment curve divided by AUC. CL\text{w} was determined from the amount of gallopamil excreted unchanged in the urine (A\text{e}) divided by AUC. The F of gallopamil was calculated from the relationship between CL\text{w} and F (Somogyi et al., 1982) previously observed.\(^3\)

\[
\frac{1}{F} = 0.89 \times CL_w + 0.42
\]

Ten measurements of each cardiovascular and electrocardiographic parameter at each time point were averaged, and the mean value is reported. This value was compared to that observed at the same time after placebo administration using a paired t test. For parameters in which significant changes relative to placebo were observed, the percentage change from the predose measurement was calculated and plotted against the gallopamil serum concentration. When hysteresis was observed, only data points on the offset part of the curve were used to analyze the concentration-effect relationship via the sigmoidal E\text{max} model (Holford and Sheiner, 1981). The model is described by the following equation, in which E is the observed effect, E\text{max} is the maximum pharmacological effect, EC\text{50} is the serum concentration eliciting half the maximum effect and N is a parameter affecting the slope of the concentration-response relationship.

\[
E = \frac{E_{\text{max}} \times C^N}{EC_{\text{50}}^N + C^N}
\]

The relationship to the overall gallopamil concentration [sum of (R)- and (S)-concentrations], the total (S)-serum concentration and the free (S)-concentration were investigated using data from individual subjects. The sigmoidal E\text{max} relationship was also calculated for the data pooled from all subjects. The data were fitted using a nonlinear least-squares regression program (Nichols and Peck, 1981).

Gallopamil pharmacokinetic parameters are reported as the mean ± S.D., with the exception of half-life, which is reported as the harmonic mean. The parameters calculated in each phase of the study were compared using the Friedman two-way analysis of variance by ranks (Siegel, 1956). (R)-Gallopamil pharmacokinetic parameters at the doses of 25 and 100 mg and pharmacodynamic parameters were calculated using the overall (R + S), and total or free (S)-gallopamil serum concentrations were compared using the Wilcoxon matched-pairs signed-rank test (Siegel, 1956). B/P values were compared using the Mann-Whitney U test (Siegel, 1956). A probability of < .05 was considered significant.

Results

Pharmacokinetics of (R)- and (S)-gallopamil administered separately. In all subjects, similar serum concentration-time profiles of (R)- and (S)-gallopamil (25 mg) were observed when the enantiomers were administered separately. Data from a representative subject are shown in figure 2. Considerable interindividual variation in the pharmacokinetic parameters of (R)- and (S)-gallopamil was observed (tables 1 and 2, respectively). After separate administration, C\text{max} > t\text{max} > AUC, CL\text{w}, t\text{1/2}, MRT and F values for (R)- and (S)-gallopamil were comparable (P > .05). The urinary recovery of (S)-gallopamil was twice (P < .05) that of the (R)-enantiomer; however, it accounted for just 0.33% and 0.15% of the dose administered, respectively. Consequently, the CL\text{w} of gallopamil was stereoselective. The mean f\text{u} of (S)-gallopamil was higher than that of (R)-gallopamil; however, the difference was not significant. The B/P values for (R)- and (S)-gallopamil were similar (R, 0.63 ± 0.09, n = 5; S, 0.52 ± 0.05, n = 4; P > .05) and substantially lower than unity.

The pharmacokinetic parameters of (R)-gallopamil after the 100-mg dose are given in table 3. There was large interindividual variation in C\text{max}, AUC and CL\text{w}. In subjects 1, 4 and 6, there were 6.9-, 7.8- and 14.6-fold increases in AUC, respectively, after the 4-fold increase in dose; however, when pooled data were considered, there was no difference (P = .102) in CL\text{w} after the 25- and 100-mg doses of (R)-gallopamil. The urinary recovery of (R)-gallopamil after the 100-mg dose was more than four times greater than that after the 25-mg dose, reflecting the higher serum concentrations of unchanged drug and a constant CL\text{w}. The f\text{u} and B/P (0.64 ± 0.11, n = 6) were similar (P > .05) after the 25- and 100-mg (R)-gallopamil doses.

After the 100-mg (R)-gallopamil dose, serum concentrations of both (R)- and (S)-gallopamil were measured in the samples at t\text{max} (0.5-5 hr; see table 3). (S)-Gallopamil concentrations were low (0.69 ± 0.28 nmol/liter) and in all subjects contributed to 0.35 ± 0.26% of the total gallopamil serum concentration, which is consistent with the high optical purity of the gallopamil enantiomers administered (0.14%). Therefore, a chiral inversion of (R)- to (S)-gallopamil was not observed in vivo.

Gallopamil serum concentrations in subject 4 were higher than those in other subjects on all study days. After administration of the individual enantiomers, serum concentrations plateaued at 15 hr postdose and did not decline in the usual manner. Consequently, t\text{1/2} values could not be estimated. The AUC was calculated to 25 hr and was not extrapolated to infinity. The CL\text{w} values of (R)- and (S)-gallopamil

\(^{3}\) Based on data from 14 healthy normal subjects after intravenous and oral administration; data on file at Knoll AG (Ludwigshafen, Germany).
were substantially lower in this subject than in the other volunteers.

Pharmacokinetics of (R)-gallopamil. Representative serum concentration-time profiles of (R-) and (S)-gallopamil after the administration of the pseudoracemate are shown in figure 3, respectively. Pharmacokinetic parameters for (R-) and (S)-gallopamil are given in tables 1 and 2. In all subjects, the (R) and (S) serum concentration-time profiles were similar; however, there was considerable interindividual variation in gallopamil pharmacokinetic parameters. No differences in Cmax, tmax, t1/2, AUC and CLo values between (R)- and (S)-gallopamil were observed. The ratio of the CLo values of the (S-) and (R)-enantiomers was 1.06 ± 0.37. A small but significant difference was noted in MRT. The urinary recovery and renal clearance values for (S)-gallopamil (263.9 ± 152.9 nmol, 0.55% dose; 25.9 ± 9.7 ml/min) were greater (P < 0.05) than those of (R)-gallopamil (163.7 ± 74.2 nmol, 0.34% dose; 14.5 ± 6.4 ml/min). The fu, of (S)-gallopamil in serum was higher (P < 0.05) than that of (R)-gallopamil. B/P value for (R)-gallopamil (0.52 ± 0.05, n = 4) was similar (P > 0.05) to that of (S)-gallopamil (0.54 ± 0.02, n = 4). In all subjects, serum (R)-gallopamil concentrations after administration of the 100-mg dose were higher than after administration of the pseudoracemate.

### Table 1

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<th>Subject</th>
<th>Cmax (nmol/liter)</th>
<th>tmax (hr)</th>
<th>t1/2 (hr)</th>
<th>AUC (nmol/liter hr)</th>
<th>CLo (ml/min)</th>
<th>F (%)</th>
<th>Ae (nmol/hr)</th>
<th>MRT (hr)</th>
<th>CLR (ml/min)</th>
<th>t1/2 (hr)</th>
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### Table 2

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<td>7.1</td>
<td>58.8</td>
<td>13.6</td>
<td>7.9</td>
<td>104.4</td>
<td>4.3</td>
<td>29.6</td>
<td>0.076</td>
</tr>
<tr>
<td>Mean</td>
<td>50.9</td>
<td>0.83</td>
<td>6.7</td>
<td>119.9</td>
<td>11.0</td>
<td>14.0</td>
<td>157.7</td>
<td>3.7</td>
<td>31.8</td>
<td>0.059</td>
</tr>
<tr>
<td>S.D.</td>
<td>34.4</td>
<td>0.34</td>
<td>106.6</td>
<td>6.0</td>
<td>11.9</td>
<td>74.2</td>
<td>0.8</td>
<td>16.5</td>
<td>0.016</td>
<td></td>
</tr>
</tbody>
</table>

### Notes

- AUC(0–25 hr): in other subjects, <5% of total AUC results from extrapolation to infinity.
- P < 0.05: (R)-gallopamil 25 mg alone vs. (R)-gallopamil 25 mg from 50 mg (RS)-gallopamil.
- Harmonic mean.
- N.D. = not determined.
The serum levels of both enantiomers were again higher in subject 4 than in the other volunteers. On this occasion, serum gallopamil concentrations declined in the usual manner, with $t_{1/2}$ values for (R)- and (S)-gallopamil comparable to those of the other volunteers (tables 1 and 2).

Effect of coadministration of gallopamil enantiomers. The serum concentrations of both enantiomers were higher when coadministered than when the same dose was administered separately (figs. 2 and 3). Consequently, $C_{\text{max}}$ and AUC for (R)- and (S)-gallopamil were higher after coadministration, and the CL$_{O_{\infty}}$ values for (R)- and (S)-gallopamil were reduced. The $F$ values of both enantiomers were enhanced. The $t_{1/2}$ and CL$_{R}$ of (R)- and (S)-gallopamil were not altered by administration of the optical antipode. A greater proportion of each dose was excreted as the unchanged drug in urine, reflecting unaltered CL$_{R}$ values and higher serum concentrations of (R)- and (S)-gallopamil. The serum protein binding and B/P for (R)- and (S)-gallopamil were comparable ($P < .05$) when the enantiomers were administered separately or together.

Gallopamil metabolism. The urinary recoveries of the enantiomers of the gallopamil metabolites after the 50-mg dose of the pseudoracemate are given in table 4. The chemical structures of these metabolites are shown in figure 1. Stereoselective metabolism of gallopamil was observed. N-Dealkylation to form D832 was the major pathway of metabolism and favored (R)-gallopamil. For the N-demethylated (D845) and O-demethylated metabolites at either the aromatic ring adjacent to the chiral center (D829) or the phenethyl aromatic ring (PR53, SZ488), metabolism of (S)-gallopamil was favored. The overall recovery of unchanged gallopamil and metabolites in the 48-hr urine samples was 14.6 ± 2.5% of

TABLE 3
Pharmacokinetic parameters of (R)-gallopamil HCl after the 100-mg dose

<table>
<thead>
<tr>
<th>Subject</th>
<th>$C_{\text{max}}$ (nmol/liter/hr)</th>
<th>$t_{\text{max}}$ (hr)</th>
<th>$t_{1/2}$ (hr)</th>
<th>AUC (liter/min)</th>
<th>CL$<em>{O</em>{\infty}}$ (liter/min)</th>
<th>$F$ (nmol/hr)</th>
<th>$A_{\infty}$ (nmol)</th>
<th>MRT (hr)</th>
<th>CL$_{R}$ (ml/min)</th>
<th>$t_{1/2}$ (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>103.3</td>
<td>0.50</td>
<td>7.7</td>
<td>187.4</td>
<td>4.3</td>
<td>23.5</td>
<td>251.8</td>
<td>4.3</td>
<td>22.4</td>
<td>0.045</td>
</tr>
<tr>
<td>2</td>
<td>51.2</td>
<td>1.50</td>
<td>5.2</td>
<td>151.2</td>
<td>21.2</td>
<td>5.2</td>
<td>242.0</td>
<td>4.2</td>
<td>26.7</td>
<td>0.057</td>
</tr>
<tr>
<td>3</td>
<td>156.7</td>
<td>1.50</td>
<td>3.7</td>
<td>339.7</td>
<td>9.4</td>
<td>11.4</td>
<td>659.7</td>
<td>4.0</td>
<td>32.4</td>
<td>0.045</td>
</tr>
<tr>
<td>4</td>
<td>380.6</td>
<td>0.75</td>
<td>N.D.</td>
<td>1295.3</td>
<td>2.5</td>
<td>37.8</td>
<td>1465.3</td>
<td>6.2</td>
<td>18.9</td>
<td>0.044</td>
</tr>
<tr>
<td>5</td>
<td>364.5</td>
<td>0.50</td>
<td>4.5</td>
<td>531.5</td>
<td>6.0</td>
<td>17.4</td>
<td>1141.3</td>
<td>3.0</td>
<td>35.8</td>
<td>0.030</td>
</tr>
<tr>
<td>6</td>
<td>438.2</td>
<td>0.75</td>
<td>5.2</td>
<td>943.8</td>
<td>3.4</td>
<td>29.0</td>
<td>1260.7</td>
<td>3.7</td>
<td>22.3</td>
<td>0.049</td>
</tr>
<tr>
<td>Mean</td>
<td>249.1</td>
<td>0.92</td>
<td>5.0</td>
<td>574.8</td>
<td>7.8</td>
<td>20.7</td>
<td>836.8</td>
<td>4.0</td>
<td>26.4</td>
<td>0.045</td>
</tr>
<tr>
<td>S.D.</td>
<td>164.5</td>
<td>0.47</td>
<td></td>
<td>465.6</td>
<td>7.0</td>
<td>11.9</td>
<td>528.2</td>
<td>1.2</td>
<td>6.5</td>
<td>0.009</td>
</tr>
</tbody>
</table>

* * P < .05: 25 mg vs. 100 mg.
* AUC(0–25 hr): in other subjects, <5% of total AUC results from extrapolation to infinity.
* Harmonic mean.
* N.D. = not determined.

Fig. 3. Serum concentration-time profile of (R)-gallopamil ($\bullet$) and (S)-gallopamil (■) after the administration of 50 mg of pseudoracemic gallopamil HCl in subject 3.

The serum levels of both enantiomers were again higher in subject 4 than in the other volunteers. On this occasion, serum gallopamil concentrations declined in the usual manner, with $t_{1/2}$ values for (R)- and (S)-gallopamil comparable to those of the other volunteers (tables 1 and 2).

TABLE 4
Cumulative urinary excretion of the enantiomers of the gallopamil metabolites and the total urinary recovery of each enantiomer (parent drug plus metabolites) in six healthy subjects after administration of 50 mg of pseudoracemic gallopamil HCl (i.e., 47.9 $\mu$mol of each enantiomer)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Substance</th>
<th>D832 (S) (R)</th>
<th>D845 (S) (R)</th>
<th>D829 (S) (R)</th>
<th>PR53 (S) (R)</th>
<th>SZ488 (S) (R)</th>
<th>Total recovery (S) (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.2</td>
<td>9.3</td>
<td>0.44</td>
<td>0.23</td>
<td>1.10</td>
<td>0.83</td>
<td>0.27</td>
</tr>
<tr>
<td>2</td>
<td>4.8</td>
<td>6.8</td>
<td>0.38</td>
<td>0.15</td>
<td>1.06</td>
<td>0.73</td>
<td>0.20</td>
</tr>
<tr>
<td>3</td>
<td>5.9</td>
<td>8.0</td>
<td>0.34</td>
<td>0.22</td>
<td>1.03</td>
<td>0.75</td>
<td>0.19</td>
</tr>
<tr>
<td>4</td>
<td>3.6</td>
<td>5.4</td>
<td>0.51</td>
<td>0.31</td>
<td>0.65</td>
<td>0.63</td>
<td>0.17</td>
</tr>
<tr>
<td>5</td>
<td>3.8</td>
<td>6.4</td>
<td>0.37</td>
<td>0.17</td>
<td>0.66</td>
<td>0.49</td>
<td>0.16</td>
</tr>
<tr>
<td>6</td>
<td>5.1</td>
<td>8.1</td>
<td>0.41</td>
<td>0.16</td>
<td>1.10</td>
<td>0.60</td>
<td>0.42</td>
</tr>
<tr>
<td>Mean</td>
<td>4.9</td>
<td>7.3</td>
<td>0.41</td>
<td>0.21</td>
<td>0.93</td>
<td>0.67</td>
<td>0.23</td>
</tr>
<tr>
<td>S.D.</td>
<td>1.1</td>
<td>1.4</td>
<td>0.06</td>
<td>0.06</td>
<td>0.22</td>
<td>0.12</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Mean $S/R$ ratio 0.66 2.14 1.38 9.15 11.26 0.83

Mean S.D. 0.05 0.58 0.24 3.61 3.11 0.04
the dose for (S)- and 17.6 ± 2.9% of the dose for (R)-gallopamil.

**Pharmacological effects.** Gallopamil was well tolerated by all subjects. Facial flushing was observed in one volunteer (subject 1) from 30 to 90 min after the administration of (S)- and (RS)-gallopamil. First-degree AV block occurred in subject 4 after 25 mg of (S)-gallopamil and in subject 5 after pseudoracemic gallopamil. After pseudoracemic gallopamil, AV dissociation without loss of rhythm occurred in subject 4 for 75 min, from 0.75 to 2 hr postdose. Predose cardiovascular and electrocardiographic parameters were similar in each subject on each study day. In addition, all parameters were within the appropriate normal range for young normotensives (fig. 4).

Consistent and substantial changes in the PR interval occurred. The maximum percent prolongation of the PR interval observed in each subject during each phase of the study is given in table 5. (S)-Gallopamil significantly prolonged the PR interval (26.6 ± 9.8%); the effect was more pronounced after pseudoracemic gallopamil (37.7 ± 17.3%).

The administration of 25 mg of (R)-gallopamil did not significantly alter the PR interval relative to placebo administration. No change in PR interval was elicited by 100 mg of (R)-gallopamil in five subjects, and although very high and comparable (R)-gallopamil concentrations were measured in subjects 4 and 5, a prolongation of the PR interval (20%) was observed only in subject 4 (fig. 5). The maximum PR interval was measured on average 1 hr after drug administration (fig. 4B), which was 10 min later than the time at which the Cmax of gallopamil was attained (table 2). Graphs of percentage change in PR interval vs. gallopamil serum concentration therefore displayed slight counterclockwise hysteresis. The sigmoidal $E_{max}$ model was used for further analysis, although this model has its limitations, especially with data after intravenous administration (Schwarz *et al.*, 1989).

The PR interval change after administration of the racemate was related to the sum of the concentration of both enantiomers (R + S), the concentration of (S)-gallopamil or the free concentration of (S)-gallopamil. The values of $E_{max}$, EC50 and N obtained when the offset data were fitted to the

**Fig. 4.** The mean of the electrocardiographic parameters (A) diastolic blood pressure, (B) PR interval, (C) blood flow and (D) plasma renin concentrations monitored in six subjects for 5 hr after the administration of placebo (C), 25 mg of (R)-gallopamil (Δ), 100 mg of (R)-gallopamil (▴), 25 mg of (S)-gallopamil (●) and 50 mg of pseudoracemic gallopamil (▵).
sigmoidal $E_{\text{max}}$ model are given in table 6 after the dose of 25 mg of (S)- and in table 7 after 50 mg of (RS)-gallopamil. The $E_{\text{max}}$ model fitted the measured data well in all subjects, as represented by subject 2 (fig. 6). After the administration of (RS)-gallopamil, an EC$_{50}$ value of 72.5 ± 70.8 nmol/liter was observed. If the (S)-gallopamil concentration alone was considered, the EC$_{50}$ value was comparable ($P > .05$ when the (S)-enantiomer was administered alone (EC$_{50}$ = 52.5 ± 60.9 nmol/liter) or as racemate (EC$_{50}$ = 41.3 ± 46.1 nmol/liter). When the pharmacologically active unbound (S)-gallopamil was considered, the EC$_{50}$ value was again similar after 25 mg of (S)-gallopamil was administered separately (2.67 ± 2.40 nmol/liter) or as 50 mg of (RS)-gallopamil (2.19 ± 2.27 nmol/liter). The relationship between effect and response was therefore not improved when plasma protein binding was also considered.

On pooling the data from all subjects, the relationship between serum concentrations of free (S)-gallopamil and PR interval change after administration of (S)- and (RS)-gallopamil was compared (fig. 7). For the pooled data, the free gallopamil EC$_{50}$ values (S; 2.15 nmol/liter; pseudoracemate, 3.84 nmol/liter) were comparable and similar to the mean of the EC$_{50}$ values observed in individual subjects. Because the relationship between (S)-gallopamil concentration and effect is comparable after 25 mg of (S)-gallopamil and 50 mg of (RS)-gallopamil, the effect observed after the racemate can be fully accounted for by the (S)-gallopamil concentration present. This finding supports the observation that (R)-gallopamil administered alone does not alter AV nodal conduction time.

Relative to placebo administration, no significant or consistent changes in the electrocardiographic parameters P wave, QRS interval, QT interval and QTc interval were observed after the administration of any gallopamil dosage form. Furthermore, heart rate, systolic blood pressure, diastolic blood pressure (fig. 4), mean arterial pressure, peripheral blood flow (fig. 4) and peripheral vascular resistance were unaltered, relative to placebo. Pretreatment plasma renin concentrations were not significantly affected by the administration of placebo or gallopamil (fig. 4).

### Discussion

Whether administered separately or together, the CLo values of (R)- and (S)-gallopamil are high and not different. Thus, the substantial first-pass metabolism of gallopamil is not stereoselective. Relative to administration of the separate enantiomers, coadministration decreases the CLo values and increases the F values of both (R)- and (S)-gallopamil. This can be attributed to a saturation of first-pass metabolism as the gallo-
pamil dose was twice as high when administered as racemate compared with the dose of the gallopamil enantiomers administered separately. This is further supported by the results after the administration of 100 mg of (R)-gallopamil; a nonlinear increase of the AUC was observed compared with 25 mg of (R)-gallopamil. From the F values that were estimated using the equation given above (F = 0.89 × Cl₀ + 0.42), the extraction ratios of (R)- and (S)-gallopamil were calculated (ER = 1 – F) and are high for both (R)-25 mg (R) = 0.90, 50 mg (RS) = 0.76] and (S)-25 mg (S) = 0.86, 50 mg (RS) = 0.77) gallopamil. Enantioselectivity is not observed when the enantiomers are administered separately or together. Importantly, the extraction ratio of both enantiomers is diminished when they are coadministered due to the first-pass metabolism of gallopamil; however, the individual pathways of biotransformation exhibited stereoselectivity to varying degrees. N-Dealkylation to D832 was the major pathway of elimination monitored and favored (R)-gallopamil (S/R 0.7). In contrast, N-demethylation to D845 favored (S)-gallopamil (S/R 2.1). O-Demethylation at both aromatic rings also favored (S)-gallopamil; however, the enantioselectivity was more pronounced at the phenethyl aromatic ring 5 (S) 0.87, 50 mg of (RS); E_max = 68.9%, EC_50 = 3.84 nmol/liter, n = .87, r^2 = .35).
rat and human liver microsomes has been investigated (Mutlib and Nelson, 1990a, 1990b). However, the authors of the in vitro study report only the rate of formation of each metabolite at two gallopamil concentrations. In vivo drug metabolism is reflected more reliably by the in vitro intrinsic clearance calculated after measuring the kinetics of metabolite formation in vitro. For the major metabolite D832, the in vitro (S/R 0.76) and in vivo data (S/R 0.66) correspond well. However, for para-O-demethylation at the aromatic ring adjacent to the chiral atom, the results differ (S/R in vitro 0.7 vs. S/R in vivo 1.4). Stereoselectivity in O-demethylation at the phenethyl aromatic ring favored (S)-gallopamil in both studies, but the degree of stereoselectivity was lower in vitro (S/R meta-3.5, para-1.5) than in vivo. In vitro, the formation of D845 was not stereoselective (S/R 1.09), which differs from the S/R ratio of 2.14 observed in vivo.

After administration of racemic verapamil, preferential metabolism of the (S)-enantiomer occurs, and the F value of this enantiomer is diminished relative to (R)-verapamil (Voigelgesang et al., 1984), which is in contrast to the results obtained with gallopamil. It is thus interesting to compare the stereoselectivity of gallopamil and verapamil metabolism. A large difference in the stereoselectivity of O-demethylation on the aromatic ring adjacent to the chiral atom was observed. For verapamil, the clearance to D703 is more enantioselective (S/R = 9.0) (Mikus et al., 1990) than the analogous formation of D829 (S/R 1.38) from gallopamil. This suggests that the additional meta methoxy group on this aromatic ring must be a steric hindrance for interaction with the active site of the enzyme catalyzing O-demethylation. The stereoselectivity of the O-demethylation at the phenethyl aromatic ring favors (S)-gallopamil at both the meta and para positions and although of negligible significance in vivo (Mikus et al., 1990), in vitro it also favors (S)-verapamil (S/R 1.2) (Kroemer et al., 1992). The formation of the major N-dealkylated metabolite favors (R)-gallopamil (D832 S/R 0.66) but (S)-verapamil (D617: S/R 5.1 in vivo; S/R 1.4 in vitro) (Kroemer et al., 1992; Mikus et al., 1990). Gallopamil and verapamil, two calcium antagonists with very similar structures, therefore differ substantially in the enantioselectivity of metabolic clearance and consequently disposition.

There was substantial interindividual variation in the CLo of both enantiomers, as has been reported for other high clearance drugs, including nitrendipine (Mast et al., 1992). In particular, the diminished clearance of gallopamil in subject 4 in each phase of the study, relative to the other volunteers, is noteworthy. Higher gallopamil serum concentrations and therefore a greater pharmacological response occurred in each phase of the study; a 20% PR-interval prolongation was also observed in this subject after 100 mg of (R)-gallopamil, but this response was substantially less than that occurring after (S)- or (RS)-gallopamil. As in other subjects, in subject 4 low concentrations of (S)-gallopamil were measured after the 100-mg dose of (R)-gallopamil, as a result of optical impurity of (R)-gallopamil, which would not be expected to elicit a pharmacological response. As the enhanced F value in Subject 4 was reproducible, first-pass metabolism of gallopamil must be impaired. The enzymes that metabolize gallopamil have not been identified. Subject 4 was an extensive metabolizer of both sparteine and mephenytoin, and therefore a deficiency of CYP2D6 (Eichelbaum and Gross, 1990) or CYP2C19 (Wilkinson et al., 1989) was not responsible for the diminished first-pass metabolism of gallopamil that we noted.

In contrast to the CLo, the plasma protein binding and renal excretion of gallopamil are stereoselective. The plasma protein binding of both enantiomers is high, within the range previously reported for racemic gallopamil in healthy volunteers (Rutledge and Pieper, 1987), and the enantiomers do not compete for protein binding sites at the concentrations studied. Whole blood concentrations of both enantiomers were substantially lower than serum concentrations, indicating that gallopamil does not preferentially associate with erythrocytes. The B/P values of (R)- and (S)-gallopamil were similar and comparable after separate and simultaneous administration, indicating that erythrocyte uptake is not enantioselective or influenced by the optical antipode.

Less than 1% of the dose of either (R)- or (S)-gallopamil was recovered in urine as unchanged drug, as has been reported previously for racemic gallopamil (Eichelbaum, 1989; Stieren et al., 1983). The urinary recovery and renal clearance of gallopamil favored the (S)-enantiomer, reflecting the higher f0 of (S)-gallopamil. Calculations using the creatinine clearance and gallopamil f0 indicated that net stereoselective renal tubular secretion of gallopamil occurred but accounted for only a negligible proportion of the total clearance of gallopamil, and competition for renal tubular secretion was observed. The renal clearance of (R)-gallopamil was comparable after the 25- and 100-mg doses, indicating that net renal tubular secretion was not saturated at the serum concentrations attained. The urinary recovery of both enantiomers was greater after (RS)-gallopamil than when the enantiomers were administered separately, reflecting the higher gallopamil serum concentrations.

Of the electrocardiographic parameters monitored, only AV node conduction was affected by gallopamil. PR-interval prolongation was observed after 25 mg of (S)- and 50 mg of (RS)-gallopamil. No change occurred after 25 mg of (R)-gallopamil or in five of six subjects after 100 mg of (R)-gallopamil. In all subjects, serum concentrations of (R)-gallopamil were higher after 100 mg of (R)-gallopamil than after 50 mg of (RS)-gallopamil and, for the pooled data, did not produce a significant prolongation of the PR interval. Indeed, when the serum concentration-effect data were analyzed using the sigmoidal Emax model, the response after the racemate could be accounted for by the (S)-gallopamil serum concentrations observed. Therefore, (R)-gallopamil does not contribute to the pharmacological response when the racemate is administered, and the PR-interval prolongation is elicited solely by the (S)-enantiomer. These data in human volunteers in vivo substantiate in vitro studies demonstrating that (S)-gallopamil is a more potent calcium antagonist than (R)-gallopamil (Bayer et al., 1975; Müller and Willsmann, 1982; van Amsterdam et al., 1990). The greater effect observed after the administration of the racemate was not caused by (R)-gallopamil directly but rather by the increased concentrations of (S)-gallopamil, which result from the saturation of first-pass metabolism by the higher dose of the racemate administered, relative to the doses of the single enantiomers.

The negative dromotropic effect of (RS)-gallopamil has been observed in patients who were administered racemic gallopamil (Markus et al., 1992; Rettig et al., 1983; Scrutinio et al., 1985). No changes in blood pressure were observed in
this investigation. Previous studies in normotensive subjects have similarly shown that gallopamil does not influence blood pressure (Brogden and Benfield, 1994). Furthermore, no change in peripheral blood flow, peripheral vascular resistance or heart rate were observed. These data confirm previous observations that phenylalkylamine calcium antagonists do not have a pronounced effect on the peripheral vasculature and thus are more cardioselective than other classes of calcium channel blockers.

Single-dose gallopamil administration also did not alter plasma renin concentrations, and verapamil also does not influence renin release (Chellingsworth and Kendall, 1988; McTavish and Sorkin, 1989).

In summary, the first-pass metabolism of gallopamil is not stereoselective but saturable as the dose is increased. (S)-Gallopamil is a potent negative chronotropic agent, whereas (R)-gallopamil does not contribute to the prolongation of the PR interval that is observed when the racemate is administered. Studies using both the individual enantiomers and the racemate of a chiral drug are therefore required to fully describe the pharmacokinetics and pharmacodynamics of a drug used clinically as a racemic mixture.

Acknowledgments

The enantiomers and metabolites of gallopamil were generously supplied by Knoll AG (Ludwigshafen, Germany). We thank Ms. Claudia Eser and Mr. Bernd Borstel for their technical expert assistance.

References


