Pharmacokinetics and pharmacodynamics of R- and S-gallopamil during multiple dosing

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Aims Using a stable isotope technique we investigated the pharmacokinetics and pharmacodynamics of gallopamil after administration of 50 mg pseudoracemic gallopamil every 12 h for 7 doses (72 h).

Methods Six male healthy volunteers were studied. After the seventh dose the pharmacokinetics and pharmacodynamics were assessed. Serum levels of gallopamil were measured by gas chromatography/mass spectrometry. Effects of gallopamil were measured by ECG recording.

Results The apparent oral clearances (R: 4.8 l min^{-1} (95% CI: 2.9–6.8); S: 5.5 l min^{-1} (95% CI: 2.5–8.5)) and half-lives (R: 6.2 h; S: 7.2 h) of R- and S-gallopamil were similar ($P > 0.05$). The serum protein binding (f_u R: 0.035 (95% CI: 0.026–0.045); S: 0.051 (95% CI: 0.033–0.069)) and the renal elimination (% of dose R: 0.49%; S: 0.71%) were enantioselective. Gallopamil had a potent effect on the PR interval (% prolongation 35.7% (95% CI: 14.0–57.3)). No changes in other electrocardiographic or cardiovascular parameters were observed.

Conclusions The pharmacokinetics and bioavailability of the racemic drug gallopamil are not stereoselective at steady-state and are therefore not substantially altered compared with the single dose administration of gallopamil.

Keywords: enantiomers, gallopamil, healthy volunteers, pharmacodynamics, pharmacokinetics

Introduction

The antianginal agent gallopamil, a phenylalkylamine calcium antagonist, is used clinically as a racemic mixture [1]. The pharmacokinetics and pharmacodynamic effects of the individual enantiomers of chiral drugs can differ [2] and in order to understand the clinical pharmacology of racemic drugs, the activity and fate of each enantiomer should be fully characterized. The disposition and pharmacological effects of R- and S- and RS-gallopamil after single dose administration in man have recently been investigated [3]. The apparent oral clearance, bioavailability and half-life of racemic gallopamil are not enantioselective after single dose administration of the racemate. The potent effect of gallopamil on AV node

conduction is stereoselective and elicited by the S-enantiomer alone.

The disposition of some drugs at steady-state can differ from that observed after single dose administration. Factors such as dose-dependent capacity limited metabolism and autoinduction of metabolism can contribute to this change [4]. The bioavailability of racemic gallopamil in patients at steady-state has been reported to be higher (22%) than after single dose administration (15%) [5], suggesting that gallopamil first-pass metabolism may be decreased after multiple dose administration [6]. R- and S-gallopamil are eliminated principally by metabolism and stereoselectivity in the pathways of metabolism has been reported both *in vitro* [7–9] and *in vivo* [3]. It is possible therefore that the change in first-pass metabolism may favour one enantiomer and enantioselective disposition at steady-state may result with emerging consequences for drug action.

The present study has investigated the pharmacokinetics and pharmacodynamics of gallopamil after administration of 50 mg gallopamil every 12 h for 7 doses (72 h). The gallopamil dosage regimen recommended is 25 or 50 mg 2–4 times daily, with a minimum dosage interval of 6 h.

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The half-lives of R- and S-gallopamil after single dose administration are 4.7 and 5.8 h, respectively [3] and steady-state should be attained within 36 h of initiation of therapy. Pseudoracemic gallopamil, coadministered unlabelled R-gallopamil and S-gallopamil labelled with two deuterium atoms, has been used in order to measure the concentration of both enantiomers using gas chromatography-mass spectroscopy. The cardiovascular and electrocardiographic effects of gallopamil have been monitored after the seventh dose and related to the concentration of the active enantiomer, S-gallopamil. The pharmacokinetics of the enantiomers at steady-state and the pharmacological responses observed have been compared with those previously reported after single dose administration of pseudoracemic gallopamil [3].

Methods

Hard gelatine capsules containing 25 mg R-gallopamil HCl or 25 mg S-[²H₂]-gallopamil HCl were supplied by Knoll AG, Ludwigshafen, Germany. Each gallopamil enantiomer was greater than 99% stereochemically and isotopically pure and a previous investigation had demonstrated that there was no significant effect of isotope labelling on the pharmacokinetics of S-gallopamil. The study was approved by the Ethics Committee of the Robert Bosch Hospital, Stuttgart. Six healthy male volunteers (age: 24–36 years, weight: 63–86 kg) all of whom had participated in an investigation of the pharmacokinetics of the enantiomers of gallopamil after single dose administration [3], gave written informed consent to participate in the study. The volunteers were medication-free for 7 days prior to the study and abstained from medications, alcohol and caffeine containing beverages throughout the study. Subject 5, the only cigarette smoker, also refrained from smoking.

Each subject was administered 25 mg R-gallopamil HCl and 25 mg S-[²H₂]-gallopamil HCl every 12 h for 7 doses. The total dose of each gallopamil enantiomer was 175 mg (335 µmol). Each dose of gallopamil was administered with 100 ml of mineral water under medical supervision. Morning doses were taken at 08.00 h after an overnight fast and the time of the first 08.00 h dose was designated time zero. A standard breakfast was eaten 3 h and lunch 5 h postdose. Dinner was taken 11 h after the morning dose and thus 1 h prior to the evening gallopamil dose. The heart rate, blood pressure (Dinamap 1846 SX, Critikon GMBH, Germany) and electrocardiogram (CS 6/12, Schiller, Switzerland) were monitored prior to each gallopamil dose and at 15 min intervals for 3 h postdose or until the PR interval had fallen to less than 200 ms and was decreasing. All subjects were encouraged to report any adverse effects.

A predose 10 ml blood sample was taken prior to the

first gallopamil dose and trough blood samples (8 ml) were taken by venepuncture prior to each subsequent gallopamil dose. The serum concentration-time profile and the pharmacological effects of gallopamil were characterized after the seventh dose of pseudoracemic gallopamil. An intravenous cannula was inserted and blood samples (8 ml) withdrawn predose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 8, 9, 11, 12, 14 and 15 h postdose, and by venepuncture at 24, 25, 30, 35 and 36 h postdose. During the first 5 h after the seventh dose, 1 ml of each blood sample was immediately transferred to EDTA tubes on ice, centrifuged and the plasma stored at –20° C until renin concentrations were measured by immunoradiometric assay (Renin IRMA Pasteur, ERIA Diagnostics Pasteur, France). The remaining blood was transferred to glass tubes after 30 min at room temperature and was centrifuged at 3500 rev min^{–1} for 10 min. The serum samples were stored at –20° C until analysed. The bladder was emptied prior to the first dose of gallopamil and all urine voided from 0 to 24, 24–48, 48–72, 72–96 and 96–108 h after the first dose was collected, the volume measured and aliquots stored at –20° C until analysis. Serum and urine concentrations of R-gallopamil and S-[²H₂]-gallopamil were measured by gas chromatography-mass spectrometry with selected ion monitoring [10]. After dose 7 the heart rate, blood pressure, electrocardiogram and peripheral blood flow in both legs (Infraton Vasoskript, Boucke, Germany) were monitored at 15 min intervals for 5 h postdose. R- and S-gallopamil protein binding in serum samples collected 2 h after the final dose of gallopamil was determined by equilibrium dialysis [11].

Data treatment

To verify that steady-state had been attained, serum concentrations observed immediately prior to both the second and sixth doses were compared with the levels prior to the seventh dose of pseudoracemic gallopamil using the Wilcoxon matched pairs signed ranks test [12]. R- and S-gallopamil pharmacokinetic parameters were determined from the serum concentration-time profile after the seventh dose of gallopamil using standard equations [4]. Absorption of the drug administration is almost complete as demonstrated with [¹⁴C]-gallopamil [5]. The area under the curve (AUC) over a 12 h dosage interval (72–84 h) was calculated via the linear trapezoidal rule. The apparent oral clearance at steady-state (CL_o) was calculated as Dose/AUC. The terminal slope (λ_z) of the log serum concentration-time profile, fitted using a weighted linear regression programme [13] (weight: 1/y), was used to calculate half-life (t_{1/2}) (0.693/λ_z). Mean residence time (MRT) was calculated as the area under the first moment curve divided by AUC. The renal

recovery (A_e) was the cumulative urinary excretion over the 108 h study period. Bioavailability (F) was calculated from the relationship between the apparent oral clearance and F [14] (Data on file, Knoll AG, Ludwigshafen, Germany).

$$1/F = 0.89 \star CL_o + 0.42$$

R- and S-gallopamil pharmacokinetic parameters are reported as mean and 95% confidence intervals (except half-life which is reported as the harmonic mean) and have been compared using the Friedman two way analysis of variance by ranks [12]. Using this test pharmacokinetic parameters have also been compared with those observed in the same subjects after single dose pseudoracemic gallopamil administration [3]. A probability of $P < 0.05$ has been considered significant.

The 10 measurements of each cardiovascular and electrocardiographic parameter at each time point were averaged and the mean values used. For individual subjects the relationship between serum concentrations of S-gallopamil and the effect (percent change in PR interval) were explored using the sigmoidal $E_{\max}$ model [15]. The offset data were fitted to the following equation by nonlinear least squares regression [13] where $E_{\max}$ represents the maximum pharmacological effect, EC_{50} the concentration producing 50% of the maximum effect and N a slope parameter influencing the shape of the fitted curve.

$$E = \frac{E_{\max} \star C^N}{EC_{50}^N + C^N}$$

For pooled data the relationship between free S-gallopamil levels and effect was examined using the log-linear model [15].

Results

Gallopamil was well tolerated by all six subjects and only Subjects 4 and 6 reported slight headaches at some time during the study.

R- vs S-gallopamil at steady-state

The trough serum concentrations of R- and S-gallopamil at the end of the first dosage interval (12 h) were lower ($P < 0.05$) than just prior to the seventh dose (Table 1). However trough levels just prior to the sixth and seventh doses were comparable ($P > 0.05$) confirming that steady-state had been attained during the study period (Table 1). The serum concentration-time profiles for R- and S-gallopamil over the whole study period in a representative subject are shown in Figure 1. The pharmacokinetic parameters calculated are given in Table 2.

In all subjects CL_o , $C_{\max}$, $t_{\max}$, MRT, F and $t_{1/2}$ of

R- and S-gallopamil were comparable ($P > 0.05$). However, the interindividual variation in the absolute value of the pharmacokinetic parameters was large. The protein binding of gallopamil was stereoselective and the free fraction of S-gallopamil was 50% greater than that of the R-enantiomer. The urinary recovery of S-gallopamil over the 108 h study period (0.71% of the dose) was significantly greater than that of R-gallopamil (0.49% of the dose).

Disposition at steady-state vs single dose administration

The serum concentration-time profiles of R- and S-gallopamil at steady-state were very similar to those previously observed after single dose administration of pseudoracemic gallopamil in the same volunteers [3]. The $C_{\max}$, $t_{\max}$, AUC, CL_o , F and f_u for both R- and S-gallopamil over a dosage interval at steady-state (SS) and after single dose (s.d.) administration were comparable ($P > 0.05$). The half-life of R-gallopamil (SS 6.2 h; s.d. 4.7 h) was significantly longer at steady-state, however, that of S-gallopamil (SS 7.2 h; s.d. 5.8 h) was comparable. MRT differed for both enantiomers (R: SS 4.4 h, s.d. 3.2 h; S: SS 5.1 h, s.d. 3.8 h). The percent of the dose of R- and S-gallopamil recovered in the urine was greater in the present study than after single dose administration (R: 0.15% S: 0.33%), however, accounted for only a small proportion of the dose.

Pharmacological effects at steady-state

All subjects were monitored closely after each dose of gallopamil. A potent effect on AV node conduction was observed after most gallopamil doses. First degree AV Block occurred in Subject 1 after the first, fifth and seventh doses; Subject 3 after the first, sixth and seventh doses; Subject 4 after the first five doses, Subject 5 after all seven doses and Subject 6 after the first, fourth, sixth and seventh doses. AV dissociation without loss of rhythm occurred in Subject 4 after the seventh dose and in Subject 6 after the third and fifth doses. There was large inter and intraindividual variation in the PR interval response after each gallopamil dose, as shown in Figure 2. After some evening doses of gallopamil the PR interval response was attenuated, as demonstrated by Subject 2. However, this effect did not occur in all volunteers (e.g. Subject 5). The maximum change in the PR interval measured in each subject after the seventh and final dose is given in Table 3. As previous studies have shown that the effect on AV-node conduction is related to the concentration of S-gallopamil and not the R-enantiomer [3], the relationship between the percent change in PR interval and the S-gallopamil concentration was explored

Table 1 Mean serum concentrations of R- and [$^2\text{H}_2$]-S-gallopamil prior to each gallopamil dose. The time of blood sampling after administration of the first gallopamil dose is given.

	Concentration (nmol l $^{-1}$)					
	12 h	24 h	36 h	48 h	60 h	72 h
<i>R</i> -gallopamil						
Mean	2.00	2.77	2.27	2.45	3.13	3.59*†
95% CI	−0.72–4.73	−0.93–6.48	0.38–4.16	0.42–4.49	0.34–5.92	0.04–7.13
[$^2\text{H}_2$]-S-gallopamil						
Mean	1.86	2.76	2.30	2.64	3.04	3.53*†
95% CI	−0.22–3.94	−0.14–5.65	0.24–4.36	0.21–5.06	0.15–5.89	0.09–6.96

* $P < 0.05$ 12 h vs 72 h.

†Not significant 60 h vs 72 h.

Figure 1 Serum concentration-time profile of R-(○) and [$^2\text{H}_2$]-S-gallopamil (●) in subject 5.

using the sigmoidal $E_{\max}$ model. The parameters obtained are given in Table 3.

No significant changes in heart rate, systolic or diastolic blood pressure, peripheral blood flow, peripheral vascular resistance, plasma renin concentrations or other electrocardiographic parameters (P wave, QRS, QT and QTc intervals) were observed for 5 h after the seventh dose of pseudoracemic gallopamil.

Effects at steady-state vs single dose

The effect of gallopamil on the PR interval at steady-state and that observed in the same subjects after a single dose of pseudoracemic gallopamil [3] can be compared. The maximum percent prolongation of the PR interval, as well as $E_{\max}$ and EC_{50} when related to S-gallopamil

Table 2 Pharmacokinetic parameters of R- and [$^2\text{H}_2$]-S-gallopamil after the seventh dose of 25 mg of R-gallopamil HCl and 25 mg [$^2\text{H}_2$]-S-gallopamil HCl.

Subject	$C_{\max}$ (nmol l $^{-1}$)	$t_{\max}$ (h)	$t_{1/2}$ (h)	AUC (nmol l $^{-1}$ h)	CL_o (l min $^{-1}$)	F (%)	MRT (h)	Ae (μmol)	f_u
<i>R</i> -gallopamil									
1	58.2	0.50	5.7	120.4	6.6	15.9	4.1	1.27	0.037
2	84.1	0.50	5.7	120.6	6.6	15.9	2.9	1.33	0.040
3	51.7	1.00	9.1	139.0	5.8	17.9	4.9	1.71	0.044
4	128.1	1.50	7.0	420.9	1.9	47.4	6.8	2.11	0.025
5	90.2	0.75	4.1	213.9	3.7	26.9	3.5	2.35	0.024
6	60.9	2.00	5.2	188.0	4.3	23.5	4.7	1.87	0.044
Mean	78.9	1.04	6.2	200.5	4.8	24.6	4.4	1.77	0.035
95% CI	48.9–108.8	0.41–1.67		80.3–320.6	2.9–6.8	12.0–37.2	3.2–5.4	1.33–2.22	0.026–0.045
[$^2\text{H}_2$]-S-gallopamil									
1	55.9	0.50	5.9	97.2	8.2	13.0	4.5	1.89	0.065
2	74.6	0.75	7.7	146.7	5.5	18.8	3.4	1.78	0.052
3	33.2	1.00	9.8	87.7	9.1	11.7	5.6	1.69	0.055
4	424.4	0.50	6.5	513.3	1.6	54.2	5.9	2.88	0.034
5	46.9	1.00	5.5	252.2	3.2	30.6	4.9	3.26	0.029
6	53.0	2.00	8.0	147.1	5.4	19.1	6.1	2.73	0.072
Mean	114.7	0.96	7.2	207.4	5.5	24.6	5.1	2.37*	0.051*
95% CI	−45.2–274.6	0.37–1.54		38.5–376.2	2.5–8.5	7.8–41.3	4.0–6.3	1.67–3.07	0.033–0.069

* $P < 0.05$: R vs S.

Figure 2 Change in PR interval monitored after each gallopamil dose in A subject 2 and B subject 5.

Table 3 The maximum percent change in PR interval (Δ PR percentage) after the seventh dose of pseudoracemic gallopamil in each subject. The parameters describing the relationship between the serum concentration of S-gallopamil and the percent change in PR interval fitted to the $E_{\max}$ model are also given.

Subject	Δ PR (%)	$E_{\max}$ (%)	EC_{50} (nmol l ⁻¹)	N	r ²
1	35.2	48.1	14.7	2.0	0.943
2	16.0	18.9	15.4	2.6	0.944
3	34.5	31.4	9.7	3.7	0.984
4	AV dis.*	18.6	44.8	9.2	0.952
5	63.6	72.9	43.4	2.3	0.639
6	29.0	46.4	49.8	1.4	0.267
Mean	35.7†	39.3	29.6	3.5	
95% CI	14.0–57.3	17.5–61.2	10.6–48.7	0.5–6.6	

*AV dis. = AV dissociation.

†n = 5.

serum concentrations were similar ($P > 0.05$). The relationship between free S-gallopamil serum concentrations and the effect in all subjects at steady-state ($E = 12.24 \cdot \log[\text{free S-gallopamil}] + 16.68$) and after single

dose ($E = 22.72 \cdot \log[\text{free S-gallopamil}] + 17.73$) of pseudoracemic gallopamil was similar.

Discussion

Chiral macromolecules can discriminate between the enantiomers of chiral drugs and thus the interaction with receptors as well as transport and binding proteins can be stereoselective. Consequently the pharmacodynamics and pharmacokinetics of the individual enantiomers of chiral drugs can differ.

In the healthy volunteers studied at steady-state the apparent oral clearances of R- and S-gallopamil were comparable. Therefore gallopamil first-pass metabolism at steady-state is not stereoselective. CL_o of both enantiomers is similar to that previously observed for racemic gallopamil in patients at steady-state (CL_o 5.1 l min⁻¹ [5]; 3.4 ± 0.7 l min⁻¹ [16]). These investigators also reported that the apparent oral clearance of gallopamil is reduced in patients at steady-state relative to values after administration of the first dose (8.2 ± 3.2 l min⁻¹ [5]; 4.9 ± 1.2 l min⁻¹ [16]), possibly due to partial saturation of first-pass metabolism [5, 6]. However the present study could not confirm these findings.

The CL_o of R- and S-gallopamil at steady-state and after single dose administration in the same volunteers [3] were similar (R: s.d. 5.9 l min⁻¹ SS 4.8 l min⁻¹ S: s.d. 5.8 l min⁻¹ SS 5.5 l min⁻¹) ($P > 0.05$) indicating that there is no change in the first-pass metabolism of either enantiomer during the 12 hourly dosage schedule used. Other pharmacokinetic parameters including $C_{\max}$, $t_{\max}$ and bioavailability also did not change with multiple dosing of gallopamil. A small but significant prolongation in the half-life of R-gallopamil was observed with multiple dosing. The half-life at steady-state was not stereoselective and no significant change in the half-life of S-gallopamil was observed. The MRT of both enantiomers was significantly longer at steady-state, however, again this change was small. These observations suggest that large consistent changes in half-life or mean residence time do not occur for either enantiomer at steady-state, relative to single dose administration. In general single dose administration does reliably predict twice daily gallopamil pharmacokinetics. The change in gallopamil bioavailability previously reported to occur at steady-state may be attributable to the sensitivity of the analytical techniques used to measure gallopamil serum concentrations [5] and relationships used to calculate pharmacokinetic parameters [16]. If analytical techniques of inadequate sensitivity are used, serum concentrations in the terminal elimination phase after single dose administration may not be measurable. The AUC reported may thus underestimate the true value and an artefactually higher clearance and lower bioavailability

will be reported relative to the steady-state values which can be accurately characterized.

Gallopamil is eliminated principally by metabolism and the major metabolites identified are conjugates of O- and N-demethylated metabolites [5, 17]. Although stereoselectivity in individual pathways of metabolism has been observed *in vitro* and *in vivo* [3, 7–9] a large proportion of the dose remains to be accounted for as identified metabolites. The lack of stereoselectivity in apparent oral clearance at steady-state indicates that the metabolism of both gallopamil enantiomers is balanced. This observation contrasts markedly with the pronounced stereoselective disposition of the related drug verapamil. Gallopamil is a methoxy-derivative of verapamil. The first-pass metabolism of verapamil is stereoselective, favouring the more potent S-enantiomer [18]. It can therefore be hypothesized that the small structural change sterically hinders the interaction of gallopamil with the stereoselective verapamil metabolizing enzyme. Further insight into the stereoselectivity of phenylalkylamine metabolism will be obtained when additional metabolites have been identified. The considerable interindividual variation in the apparent oral clearance and thus bioavailability of gallopamil in the six volunteers studied presumably reflect differences in the activity of gallopamil metabolizing enzymes. The high bioavailability of both enantiomers noted in Subject 4 (R: 47.4%; S: 54.2%) was also observed after single dose administration and has been discussed previously [3].

The high serum protein binding and low renal excretion of gallopamil at steady-state are stereoselective. These differences at steady-state confirm the stereoselectivity previously observed after administration of a single dose of pseudoracemic gallopamil [3]. The higher free fraction of S-gallopamil is a consequence of interactions with both albumin and α_1 -acid glycoprotein [11], and contributes to the higher renal excretion of S-than R-gallopamil observed.

Gallopamil was well tolerated by all the volunteers with no subjects experiencing any symptoms in association with the potent effect on AV node conduction. No significant changes in electrocardiographic parameters other than the PR interval, heart rate, blood pressure, peripheral blood flow, peripheral vascular resistance or plasma renin concentrations occurred. This result is consistent with our observations after the single 50 mg dose of pseudoracemic gallopamil [3]. This effect on AV node conduction has also been reported in patients administered gallopamil [19, 20]. As many patients take gallopamil without reporting adverse effects then the PR interval prolongation appears to have only limited adverse sequelae. Nevertheless the clinical consequences of this potent effect deserve further study. The PR interval prolongation observed varied over the seven doses

administered. There was a trend to a lesser effect after the evening dose of gallopamil which was taken 1 h after dinner. Gastric emptying time may be delayed by food and for a drug with a high extraction ratio such as gallopamil, first-pass metabolism may be enhanced resulting in lower peak serum concentrations and attenuated pharmacological effects.

The effect of gallopamil on AV node conduction at steady-state and after single dose administration was comparable. Therefore, the dosage regimen used does not result in either tolerance or sensitization. In all subjects no effect was measurable prior to the next dose (12 h after the previous dose) and the PR interval returned to baseline values within 5 h after the seventh dose. Therefore, the dosage regimen used is analogous to repeated single dose administration. If the PR interval is an appropriate marker of therapeutic efficacy, 12 hourly dosing will not maintain the desired response throughout a dosage interval. The slow release gallopamil dosage form now available may therefore be more appropriate for twice daily gallopamil dosing.

In summary this study has established that the pharmacokinetics and bioavailability of the racemic drug gallopamil are not stereoselective at steady-state. Furthermore, dosing gallopamil to steady-state does not substantially alter the pharmacokinetics or pharmacodynamics of gallopamil relative to single dose administration. Stereoselective serum protein binding and renal clearance of gallopamil occur after single dose administration and during steady-state.

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