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**Title:** A question based approach to drug development  
**Issue Date:** 2003-09-10
CHAPTER 7


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Funded by: Institut de Recherches Internationales Servier (I.R.I.S.)

Concentration-effect relationships of two rilmenididine single-dose infusion rates in hypertensive patients
Abstract

OBJECTIVES The current study was designed to assess the concentration-effect relationships for the anti-hypertensive effects of rilmenidine in patients to aid in the design of an optimised concentration profile of a sustained release formulation.

METHODS This was a placebo controlled, randomised, double-blind, two-way partial cross-over, study in subjects with hypertension. Twenty-six patients were randomised to receive two of three possible 12-hour infusion regimens, each consisting of a loading phase (2 h) and a maintenance phase (10 h): Low Profile infusion (total dose of rilmenidine 1.45 mg), high profile (total dose 3.3 mg) or placebo. Drug plasma concentrations, adverse events, blood pressure and heart rate, and visual analogue scales were measured frequently up to 24 hours after dosing. Salivary flow was determined up to 15 hours.

RESULTS The high concentration profile was well tolerated and still produced a significant blood pressure reduction of 10.4/5.8 mmHg after 24-hours. After 24 hours, the low concentration profile showed no significant effects on blood pressure compared to placebo. Decreases in salivary flow were -36% for the high infusion and -20% for the low profile compared to placebo. Pharmacokinetic-pharmacodynamic analyses show infusion rate independent linear concentration-dependent reductions in DBP and salivary flow up to the maximum observed rilmenidine concentration for both infusions.

CONCLUSIONS The high concentration profile was well tolerated and still produced a significant blood pressure reduction after 24-hours. Pharmacokinetic-pharmacodynamic relationships were linear and unaffected by the rate of infusion. These results should aid in the design of an optimal slow release profile.

Introduction

Rilmenidine (2-(dicyclopromethyl)-amino-2-oxazoline) is a centrally acting anti-hypertensive with binding selectivity to the I1 imidazoline receptors over α2-adreno-receptors. It has dose (concentration)-dependent blood pressure lowering effects above 0.5 mg in both healthy and hypertensive subjects. Rilmenidine is registered in several European countries.
at a recommended dose of 1 tablet of 1 milligram once or twice daily. Clinical experience indicates that with 1 mg dosing blood pressure control might not be maintained for 24 hours per day in all patients. Twenty-four hour monitoring of the effects of 1 mg rilmenidine in 80 hypertensive patients after 4 weeks treatment with this dosage suggested a significant duration of action of 14 hours. In a study of 146 patients with hypertension (95 < diastolic blood pressure [DBP] < 115mmHg), trough level blood pressure control was considered inadequate in 56% of subjects after 4 weeks of treatment. An unspecified number of these patients became adequately controlled after increasing the dosing frequency to 1 mg twice daily. This dosage regimen is less acceptable during chronic treatment, while on the other hand elevating the dose of once-daily administration may increase the incidence of peak concentration-related side-effects, such as sedation and dry mouth (xerostomia).

A sustained release formulation of the drug could maintain plasma levels in between a minimum effective (anti-hypertensive) concentration and a maximum non-sedative peak level. In addition to the plasma concentrations, the rate of increase of concentration may also influence the effect. The classic example is provided by Kleinbloesem et al who demonstrated that a high rate of increase of nifedipine concentrations did not lead to a blood pressure reduction in healthy volunteers, contrary to a low rate of increase of nifedipine concentrations. However, a previously performed study showed no influence of the rate of infusion of rilmenidine on both blood pressure and development of side-effects. The current study was part of several investigations aimed at the design of an optimal slow release profile. The present study aimed to establish minimum anti-hypertensive 24 hour trough concentrations in hypertension, and to identify pharmacokinetic / pharmacodynamics relationships that could aid in the design of an optimal controlled release concentration profile. The low profile had a plateau phase with estimated minimum effective concentrations. The high profile was designed to reach a plateau phase with estimated maximum tolerated concentrations, and a minimum effective trough level.

**Methods**

**Design**

This was a placebo controlled, randomised, double-blind, double-dummy, single-dose, two-way partial cross-over, monocentric study in subjects with hypertension, with a minimum washout period of four days.
Subjects

Hypertensive subjects, treated with a maximum of two different anti-hypertensive drugs, gave signed informed consent to participate in this non-therapeutic study. Patients were included after their treating physicians were informed. After a general health screen (during which relevant additional conditions were excluded, including causes for secondary hypertension or hypertensive complications) all anti-hypertensive agents were withdrawn (gradually in the case of β blockers), while blood pressure was monitored regularly. After return of diastolic blood pressure (dbp) to values between 95-115 mmHg, patients were scheduled for their first study occasion within five days following the detection of hypertension. Subjects who remained normotensive or whose blood pressure were higher than 115 mmHg on two consecutive occasions or once above 120 mmHg, were referred to their treating physicians, and excluded from further participation. The study was approved by the Medical Ethics Review Board of Leiden University Medical Center, and performed according to the principles of the Helsinki Declaration.

Treatments

Hypertensive patients were randomised to receive two of three possible 12-hour infusion regimens, each consisting of a loading phase (2 h) and a maintenance phase (10 h):

**Low Profile infusion:** (estimated minimum effective plateau phase of 2-3 µg/L): a constant rate infusion (14 mL/h) of a 25.3 mg/L rilmenidine solution, 0.35 mg/h over 2 hours followed by a ten hour constant rate infusion (3.0 mL/h) of the 25.3 mg/L rilmenidine solution, 0.075 mg/h. The total dose of rilmenidine infused was 1.45 mg. The infusion regimen was modelled, based on the maintenance of an estimated minimum effective peak level of approximately 2.9 µg/L for ten hours, leading to a trough concentration of approximately 1.0 µg/L after 24 h.

**High Profile infusion:** (estimated maximum tolerated plateau phase of 6-7 µg/L): a constant rate infusion (14 mL/h) of a 56.6 mg/L rilmenidine solution, 0.8 mg/h over 2 hours followed by a ten hour constant rate infusion (3.0 mL/h) of the 56.6 mg/L rilmenidine solution, 0.17 mg/h. The total dose of rilmenidine infused was 3.3 mg. The infusion regimen was modelled, based on the maintenance of an estimated maximum tolerated peak level of approximately 6.5 µg/L for ten hours, and an estimated minimum effective trough concentration of approximately 2.3 µg/L after 24 h.
**Placebo infusion:** a constant rate infusion (14 mL/h) of sodium chloride, 0.9% over 2 hours followed by a ten hour constant rate infusion (3.0 mL/h) of NaCl 0.9%. The total volume of NaCl 0.9% infused per subject was 58 ml.

A syringe infusion pump (Harvard, model 22 Harvard Electronics, South-natick, Mass, USA) was used to infuse one syringe of 40 ml during the loading phase. During this time, a one-lead telemetric **ECG**-recording was obtained. Subsequently, a volumetric infusion pump (Sigma 6000+, Stöpler Instrumenten & Apparaten b.v., Utrecht, The Netherlands) was used to administer during the maintenance phase from 2 to 12 hours. The infusion syringes and bottles were connected to the iv cannula via a line that was primed with the rilmenidine solution prior to the start of the infusion.

**Hæmodynamics**

Blood pressure and heart rate were measured with an automated blood pressure monitor (**MPV1072**, Nihon Kohden, Japan), which displays an average value for two sequential (duplicate) measurements at each time point. All measurements were made after the subject had been in a semi-recumbent position for at least 5 minutes.

**Visual Analogue Scales**

Visual analogue scales (**VAS**) as originally described by Norris were previously used to quantify subjective effects of benzodiazepines. From the set of sixteen lines three factors were derived as described by Bond and Lader, corresponding to alertness, mood and calmness. These factors were used to quantify subjective drug effects.

**Salivary Flow**

Saliva flow was estimated by measuring the weight increase of three dental rolls put into the oral cavity over a period of 3 minutes. The dental rolls and accompanying collection tubes used for this measurement were Sarstedt neutral **Salivettes®** (Sarstedt, Etten Leur, The Netherlands). For each measurement three dental rolls and a collection tube were weighed together. Subsequently, one roll was placed sublingually and the other two rolls were
positioned between each lower gum and cheek. After 3 minutes, the dental rolls were immediately put in their collection tubes and weighed later on the same day.

**Telemetric electrocardiography**

During the first hour of the infusion, a one-lead telemetric ECG-monitoring was performed using the Nihon Kohden Lifescope II telemetric recording system (Nihon Kohden Europe, Amsterdam, The Netherlands).

**Measurement times**

For the first fifteen hours after the start of the infusion and 23 and 24 hours, drug plasma concentrations, adverse events, blood pressure and heart rate, and visual analogue scales were measured every hour. An additional blood sample was obtained after 33 h. Salivary flow was determined at 0, 1, 2, 4, 8, 12 and 15 hours.

**Analyses**

**Pharmacodynamics**  Pharmacodynamic parameters were compared between treatments by calculating the area under the effect curve over 0-15hrs (using the linear trapezoidal rule on protocol times) and dividing this area by the corresponding time interval. The result is a weighted average response.

These areas-under-the-effect-curves (AUECS) were compared between treatments using an analysis of variance for cross-over design taking into account treatment, period and subject effects. Carryover was assumed absent because of the sufficiently long washout period. Treatment response was quantified using Least Square Means with associated standard errors. Contrasts between the treatments were calculated within the ANOVA model and are reported with 95% confidence intervals. Calculations were performed using SAS for Windows V6.10 (SAS Institute, Inc., Cary, NC, USA) and SPSS for Windows V10.0.7 (SPSS, Inc., Chicago, IL, USA).

**Pharmacokinetics**  Rilmenidine plasma levels were measured by using a gas chromatographic/mass spectrometric method. The limit of detection was 0.3 ng/ml and the linearity of the assay has been checked over
a range of 0.3 - 2 ng/ml. The average assay precision (coefficient of variation) is approximately 7% while the average assay accuracy (percentage of error) is 4%. The rilmenidine pharmacokinetics were described using a two-compartment model with constant coefficient of variation intra-individual error, using NONMEM version V (GloboMax LLC, Hanover, Md), applying the first order conditional estimation (FOCE) method with the ‘interaction’ option.

**PHARMACOKINETICS/PHARMACODYNAMICS (PK/PD)**

PK/PD modelling with SBP, DBP and salivary flow as effect measures was performed. The average placebo profiles for these measures indicated a clear placebo response. Placebo correction was therefore implemented by subtracting the average placebo profile from the active treatment profiles at corresponding timepoints. The empirical Bayes estimates from the PK analysis were used to generate predicted rilmenidine concentrations. For each timepoint the estimated rilmenidine concentration was plotted against the placebo corrected pharmacodynamic response. A linear concentration-effect model was estimated because individual and average graphs did not suggest any other model. Hysteresis was not apparent and therefore a direct concentration-effect relationship was assumed. Estimates were obtained for slopes and intercepts for the low treatment with difference estimates for the high treatment. A common additive between subject variability was assumed for both treatments. Residual variability was also assumed additive. First-order conditional estimation (FOCE) was used and 95% confidence intervals (95% CI) for the difference estimates between low and high treatment were calculated using population mean ± 2 times the approximate standard error as obtained from the analysis. Data management was performed using SPSS for Windows V10.0.7 (SPSS, Inc., Chicago, IL, USA).

**Results**

**Subjects**

Forty-five subjects gave written informed consent for participation in the study. Six subjects did not comply with the screening criteria: five for obesity and one for use of more than two anti-hypertensives. After antihypertensive withdrawal, eleven subjects did not comply with the inclusion criteria: seven kept DBP below 95 mmHg, one withdrew for personal reasons, and three developed DBP above 120 mmHg. Twenty-eight Caucasian subjects were included in the study (18 males, 10 females) after withdrawal of co-medication for 1-6 weeks. These subjects were 53.7 years of age (range 38-65...
years), with an average weight of 83.4 kg (range 59-104.5 kg) and an average height of 173.9 cm (range 161-190.4 cm). The average blood pressure at inclusion was 175/102 mmHg (ranges SBP 155-192, DBP 96-114 mmHg). From the 28 included patients, two subjects dropped out. One subject took disallowed concomitant medication throughout the study and the other subject withdrew for personal reasons. The study population therefore comprised twenty-six (26) completed and analysed subjects.

**Pharmacokinetics**

The time-concentration profiles for the two infusions are shown in Figure 1. Average clearance was 23.7 L/hr with a standard error of the mean (SEM) of 1.25 L/hr and an inter-individual variability as coefficient of variation (ICV) of 33%. Central volume was estimated as 213 L (SEM 33.3 L, ICV 27%) and the peripheral volume was 104 (SEM 39.4 L, ICV 49%). The residual error was 11.6%.

**Figure 1**  
Time-concentration profiles (Mean + SD) for low- (●) and high profile (▲) rilmenidine infusions
Hæmodynamics

The overall responses of the hæmodynamic parameters represented by time-corrected auecs for the 0-15h period and contrasts between the three treatments are shown in table 1. Average time effect curves are shown in figure 2. No significant effects were observed for heart rate.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low infusion (n=19)</th>
<th>High infusion (n=20)</th>
<th>Placebo (n=13)</th>
<th>High vs Placebo</th>
<th>Low vs Placebo</th>
<th>High vs Low</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LSM</td>
<td>SE</td>
<td>LSM</td>
<td>SE</td>
<td>Delta (95% CI)</td>
<td>Delta (95% CI)</td>
</tr>
<tr>
<td>Systolic bp (mmHg)</td>
<td>155.1 ± 1.63</td>
<td>138.6 ± 1.57</td>
<td>161.3 ± 2.14</td>
<td>-22.7 * (-28.5, -16.9)</td>
<td>-6.2 * (-12.1, -0.3)</td>
<td>-16.6 * (-21.3, -11.8)</td>
</tr>
<tr>
<td>Diastolic bp (mmHg)</td>
<td>89.5 ± 0.94</td>
<td>79.7 ± 0.91</td>
<td>92.8 ± 1.23</td>
<td>-13.1 * (-16.5, -9.8)</td>
<td>-3.3 (-6.7, 0.1)</td>
<td>-9.8 * (-12.6, -7.1)</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>66.7 ± 0.86</td>
<td>74.2 ± 0.83</td>
<td>65.4 ± 1.12</td>
<td>-1.2 (-4.2, 1.9)</td>
<td>1.3 (-1.9, 4.4)</td>
<td>2.4 (-5.0, 0.1)</td>
</tr>
<tr>
<td>Vas alertness (mm)</td>
<td>69.8 ± 1.54</td>
<td>70.1 ± 1.48</td>
<td>72.1 ± 2.01</td>
<td>-2.0 (-7.4, 3.4)</td>
<td>-2.2 (-7.8, 3.3)</td>
<td>-4.2 (-4.3, 4.7)</td>
</tr>
<tr>
<td>Vas mood (mm)</td>
<td>76.8 ± 1.24</td>
<td>79.1 ± 1.20</td>
<td>78.8 ± 1.62</td>
<td>0.3 (-4.1, 4.7)</td>
<td>-2.0 (-6.5, 2.5)</td>
<td>2.2 (-1.4, 5.9)</td>
</tr>
<tr>
<td>Vas calmness</td>
<td>77.0 ± 1.16</td>
<td>79.9 ± 1.12</td>
<td>77.7 ± 1.52</td>
<td>1.1 (-3.0, 5.2)</td>
<td>-0.6 (-4.8, 3.6)</td>
<td>1.7 (-1.7, 5.1)</td>
</tr>
<tr>
<td>Salivary flow (mL·3min⁻¹)</td>
<td>1.89 ± 0.11</td>
<td>1.50 ± 0.11</td>
<td>2.37 ± 0.15</td>
<td>-0.87 * (-1.27, -0.48)</td>
<td>-0.48 * (-0.89, -0.07)</td>
<td>-0.39 * (-0.72, -0.07)</td>
</tr>
</tbody>
</table>

The average baseline blood pressures were hypertensive and quite similar among the three treatment groups. At baseline, the average SBP/DBP varied between 161.5/92.6 and 168.3/98.3 mmHg. Overall blood pressures (time-corrected auecs 0-15h) diminished slightly during placebo, to average values of 161.3 ± 2.1 mmHg systolic, and 92.8 ± 1.2 mmHg diastolic (least square means and standard errors). Slightly stronger overall blood pressure reductions occurred with the low profile infusion, to 155.1 ± 1.6 mmHg for systolic and 89.5 ± 0.9 mmHg for diastolic blood pressure. The effects of the high profile infusion regimen were much stronger: the average systolic values over the 0-15h period dropped to 138.6 ± 1.6 mmHg, and the diastolic pressure to 79.7 ± 0.9 mmHg. The contrasts between the different treatments showed
statistically significant differences between placebo on the one hand and the low and the high profile rilmenidine treatments on the other; and between the two active treatments. No differences in heart rate response were found between the three treatments.

**Figure 2**

Time-effect profiles (Mean + SD) for diastolic blood pressure for placebo- (○), low- (●) and high profile (▲) rilmenidine infusions

The high profile infusion regimen resulted in good blood pressure control over the 0–15h period, but blood pressure slowly increased while the subjects remained in the research unit over the next nine hours. As shown in figure 2, the average blood pressures were still reduced twenty-four hours after the start of the placebo infusion, compared to the baseline values: systolic values were 162.8 ± 3.2 mmHg and diastolic pressure was 92.6 ± 2.0 mmHg (least square mean and standard error). The effect of the high profile infusion regimen after 24 hours differed significantly from placebo: blood pressure was 152.4 ± 2.5 mmHg systolic and 86.8 ± 1.5 mmHg diastolic, and the contrast with placebo was 10.4 (1.4, 19.4) mmHg and 5.8 (0.3, 11.3) mmHg, respectively (difference and 95% confidence interval). The average blood pressure at 24 hours after the start of the low profile infusion was 157.2 ± 2.4 mmHg systolic and 89.8 ± 1.5 diastolic, which did not differ significantly from the two other treatments. The difference from placebo was 5.7 (-3.3, 14.6) mmHg systolic and 2.8 (-2.7, 8.3) mmHg diastolic.
Pharmacokinetics/pharmacodynamics (PK/PD)

PK/PD parameter estimations for SBP, DBP and salivary flow are represented in table 2. The average placebo-corrected PK/PD relationships are presented in figure 3 for DBP and figure 4 for salivary flow. All three parameters (SBP, DBP and salivary flow) showed linear concentration-effect relationships. No significant differences were observed between the low and the high infusion for both slopes and intercepts for all effect parameters.

**Table 2**

PK/PD parameters using empirical Bayes estimates vs placebo corrected diastolic blood pressure and salivary flow. Population average (Mean), standard error of the population average (SEM), 95% confidence intervals (95% CI) and inter-individual variability as standard deviation (IISD).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SEM</th>
<th>95% CI</th>
<th>P</th>
<th>IISD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept (mmHg) Low</td>
<td>3.85</td>
<td>0.23</td>
<td>-13.1, 5.8</td>
<td>NS</td>
<td>11.9</td>
</tr>
<tr>
<td>High</td>
<td>0.23</td>
<td>0.23</td>
<td>-13.1, 5.8</td>
<td>NS</td>
<td>11.9</td>
</tr>
<tr>
<td>Difference</td>
<td>-3.62</td>
<td>4.71</td>
<td>-13.1, 5.8</td>
<td>NS</td>
<td>11.9</td>
</tr>
<tr>
<td>Slope (mmHg)/(ng/mL) Low</td>
<td>-3.01</td>
<td>2.17</td>
<td>-3.8, 1.3</td>
<td>NS</td>
<td>2.17</td>
</tr>
<tr>
<td>High</td>
<td>-4.27</td>
<td>2.17</td>
<td>-3.8, 1.3</td>
<td>NS</td>
<td>2.17</td>
</tr>
<tr>
<td>Difference</td>
<td>-1.26</td>
<td>1.28</td>
<td>-3.8, 1.3</td>
<td>NS</td>
<td>2.17</td>
</tr>
<tr>
<td>Residual error (sd; mmHg)</td>
<td>11.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Diastolic blood pressure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept (mmHg) Low</td>
<td>0.243</td>
<td></td>
<td>-8.2, 2.9</td>
<td>NS</td>
<td>1.15</td>
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<tr>
<td>High</td>
<td>-2.38</td>
<td></td>
<td>-8.2, 2.9</td>
<td>NS</td>
<td>1.15</td>
</tr>
<tr>
<td>Difference</td>
<td>-2.62</td>
<td>2.77</td>
<td>-8.2, 2.9</td>
<td>NS</td>
<td>1.15</td>
</tr>
<tr>
<td>Slope (mmHg)/(ng/mL) Low</td>
<td>-1.39</td>
<td></td>
<td>-2.3, 0.6</td>
<td>NS</td>
<td>0.00</td>
</tr>
<tr>
<td>High</td>
<td>-2.23</td>
<td></td>
<td>-2.3, 0.6</td>
<td>NS</td>
<td>0.00</td>
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<tr>
<td>Difference</td>
<td>-0.837</td>
<td>0.736</td>
<td>-2.3, 0.6</td>
<td>NS</td>
<td>0.00</td>
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<tr>
<td>Residual error (sd; mmHg)</td>
<td>6.69</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Salivary flow</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept (mL/3min) Low</td>
<td>-0.011</td>
<td></td>
<td>-1.3, 1.0</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>-0.173</td>
<td></td>
<td>-1.3, 1.0</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>-0.162</td>
<td>0.559</td>
<td>-1.3, 1.0</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Slope (mL/3min)/(ng/mL) Low</td>
<td>-0.247</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>High</td>
<td>-0.152</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference</td>
<td>0.0948</td>
<td>0.105</td>
<td>-0.12, 0.30</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Residual error (sd; mL/3min)</td>
<td>0.682</td>
<td></td>
<td></td>
<td></td>
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</tr>
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</table>

**Section 2: Developing a New Formulation - Chapter 7**
**Figure 3** Concentration rilmenidine-diastolic blood pressure profiles (Mean ± SD) for low- (●) and high profile (▲) rilmenidine infusions

**Figure 4** Concentration rilmenidine-saliva production profiles (Mean ± SD), low- (●) and high profile (▲) rilmenidine infusions
Safety

No serious adverse events occurred during the study.

**SEDATION, ALERTNESS, MOOD OR CALMNESS** The contrasts between the different treatments on visual analogue scales are shown in table 1. There were no significant differences between the placebo-, the low profile- or the high profile infusions for the three different scores derived from the visual analogue scales. The visual analogue scale scores during the placebo-infusion were quite variable, which precluded the demonstration of any effects of rilmenidine. Sedation was reported by 21 of the 26 subjects during any stage of the study since selection. Mild sedation was reported by 4/13 subjects during the placebo occasion (31%), and by 13/19 and 13/20 subjects during the low and high profile rilmenidine treatments (65-68%). Seven subjects reported sedation on both rilmenidine occasions. Three subjects reported sedation during one of the rilmenidine infusions and placebo infusion (one during the low profile infusion and placebo infusion, one during the high profile infusion and the placebo infusion and one during the high profile infusion, the placebo infusion and the pre-dosage period). Nine subjects reported sedation on one of the two rilmenidine occasions (five subjects during the low profile infusion and four subjects during the high profile infusion).

**DRY MOUTH** The overall responses on the salivary flow represented by time-corrected areas-under-the-effect-curves (AUECs) for the 0-15h period and contrasts between the three treatments are shown in table 1. The contrast between the different treatments indicated that the average saliva production differed significantly between the placebo infusion, the low profile infusion and the high profile. The average saliva production over the 0-15h period was 1.50 ± 0.11 ml·3min⁻¹ with the high profile (-36%), and 1.89 ± 0.11 ml·3min⁻¹ with the low profile infusion (-20%), compared to 2.37 ± 0.15 ml·3min⁻¹ with placebo (mean ± standard error). Spontaneous reports of dry mouth (xerostomia) were only slightly more prevalent with rilmenidine (on 4/19 low and 5/20 high profile occasions, 21 and 25%, respectively) than with placebo (on 2/13 occasions, 15%).

**HEADACHES** Headaches occurred frequently during all stages of the study. Three subjects had headaches during the placebo occasion, but two of these also had headaches during the pre-treatment and washout periods. During the low profile infusion, 13 subjects developed headache, three of whom had similar complaints before and after treatment, and one only
during the washout period. Five patients had headaches with the high profile treatment, two of whom also complained of headache during either the pretreatment or the washout period.

**TELEMETRIC ELECTROCARDIOGRAPHY** No clinically significant ECG-changes or heart rate changes were noted by telemetric ECG monitoring in any patient, during the first hour of the rilmenidine- or placebo-infusions.

**Discussion**

Both rilmenidine treatments produced demonstrable anti-hypertensive effects. The low infusion profile was aimed to maintain a 10-hour plateau at estimated minimum effective concentrations for around 10 hours. Even so, a mean hypotensive effect of 5.7/2.8 mmHg still existed twelve hours after the low dose infusion was stopped (24 hours after the start of the infusion), although the differences form placebo were not statistically significant. These results are difficult to compare to the clinical effects of anti-hypertensive agents, because clinical trials usually deal with prolonged treatment, and blood pressure reduction may gradually develop over time. The Veteran Affairs Cooperative Study Group on Anti-hypertensive Agents for instance reported systolic/diastolic changes from baseline in the order or 11-16/10-12 mmHg after six weeks of treatment with a variety of anti-hypertensive drugs. Compared to a blood pressure reduction of 5/3 mmHg with placebo in the same study, this would indicate a net chronic anti-hypertensive effect in the order of 6-11/7-9 mmHg, compared to an acute reduction of 6.2/3.3 mmHg (on average over 24 hours), found in the present study after short-term infusion of a low dose of rilmenidine.

The effects of the high profile rilmenidine infusion were more pronounced. Average blood pressures of 138.6/79.7 over the fifteen-hour period after start of the infusion are virtually normotensive. Compared with the effects of placebo, an average anti-hypertensive effect of 10.4/5.8 mmHg still existed 12 hours after infusion was stopped (24 hours after the start of the infusion) and continued to be statistically significant. The average blood pressure of 152.4/86.8 mmHg at this time was borderline hypertensive on systolic blood pressure, and 5/19 patients were still normotensive (defined as a blood pressure below 140/90), compared to 1/13 with placebo and 2/19 after the low rilmenidine profile infusion. Assuming that blood pressure would improve further with prolonged treatment, as seen with most anti-hypertensives, it seems that the high profile dose of 3.3 mg of rilmenidine...
may be efficacious in most patients. This dose is higher than the currently recommended dose of 1-2 mg/day. Obviously, this would need to be confirmed in clinical studies, because the effects may still increase during prolonged treatment.

The occurrence of side effects could pose limitations on the administration of higher doses of rilmenidine treatment. Nevertheless, salivary flow displayed a dose-related reduction, and the time-effect profiles corresponded linearly to the average predicted time-concentration profiles as shown in figure 4. The clinical relevance of these findings is uncertain, since spontaneous reports of dry mouth were only slightly more prevalent. Mild sedation was more often reported during the low and high profile rilmenidine treatments compared to placebo but this difference between placebo and rilmenidine did not recur in the vas scores measuring alertness, mood or calmness. This was largely attributable to a larger than expected variability of vas-scores, as shown by the wide variety in responses during placebo treatment. All subjects received standardised instructions about the visual analogue scales, but there may have been a partial lack of understanding of the purpose of the scales. This instrument has been developed for drug studies in young healthy volunteers, who form a generally well-educated, co-operative and homogeneous group. Patients not only differ widely in social and educational background, but also in their perception of the study. The patients’ preoccupation with the therapeutic effects of the drug during the study is likely to have influenced their capability and motivation to adopt the self-reflective attitude needed to fill in the visual analogue lines. The influence of circumstances on the sensitivity of visual analogue scales is well-known: healthy subjects readily reported the sedative effects of diphenhydramine 25 mg on visual analogue scales in the laboratory, whereas the same subjects did not indicate any sedation on the scales with doses below 100 mg during a driving test. At least for α₂-adrenoceptor agonists like clonidine, this apparent methodological discrepancy may be due to the fact that the attenuation of attention under resting condition caused by clonidine is overcome by arousal. Methods other than subjective assessments, such as saccadic eye movements where circumstances are kept more constant, are more sensitive to sedation than visual analogue lines, and showed linear concentration-effect relationship up to concentrations of 8.43 ng/ml in healthy volunteers. However, the influence of arousal on attention could also indicate that reduction of saccadic peak velocity under laboratory conditions would overestimate the level of sedation during clinical treatment, i.e. under every-day circumstances. Also, tolerance to sedation may develop during chronic treatment, which was not assessed in this single repeated dose study.
The results of this study combined with additional investigations of the effects of different infusion rates on blood pressure, salivary flow and saccadic peak velocity in healthy volunteers and the evaluation of a sustained release profile \textit{in vivo} are very helpful in assessing the benefits of a controlled release formulation in an early stage of drug development. The data from the current study suggest that a sustained mean plasma concentration of rilmenidine circa 4–6 ng/mL will be needed to permit once daily monotherapy with rilmenidine and to achieve modern therapeutic goals of $\text{SBP}<140$ and $\text{DBP}<80$ mmHg. Further multiple dose studies of oral sustained release tablets in patients should be performed to confirm adequate sustained blood pressure control. Furthermore, potential tolerance to side effects over an extended treatment period should be investigated to define the optimal therapeutic window of a new sustained release formulation.
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