A question based approach to drug development

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CHAPTER 8

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Pharmacokinetic / pharmacodynamic assessment of tolerance to central nervous system effects of a 3 mg sustained release tablet of rilmenidine in hypertensive patients

Abstract

AIMS Previous single dose studies showed clear blood pressure lowering effects of a potential sustained release profile rilmenidine, with concentration dependent effects on the central nervous system. The aim of this study was to evaluate potential changes in concentration-effect-relationships for these central nervous system effects during a 4-week treatment period with an experimental sustained release (sr) formulation of rilmenidine 3 mg once daily in mild to moderate hypertensive patients.

METHODS Fifteen mild to moderate hypertensive patients were withdrawn from their own anti-hypertensive treatment (gradually in the case of beta-blockers) and switched immediately to a 4 week rilmenidine SR treatment. The central nervous system effects of the treatment were evaluated using saccadic eye movements for sedative effects and visual analogue scales for subjective effects on alertness, mood and calmness. Measurements for pharmacokinetic (PK) and pharmacodynamic (PD) evaluations were performed on the first day of the treatment period and repeated after one week and four weeks of treatment.

RESULTS No serious or severe adverse events were reported. Blood pressure control remained adequate. Drug concentrations increased during the study, whereas treatment related reductions in saccadic peak velocity (SPV) remained similar on all three study days. The slopes of the concentration-effect-curves for SPV remained unchanged throughout the study, while the intercepts tended to increase as a result of increased pre-dose values. Similar effects were observed for visual analogue scales for alertness: pre-dose values increased significantly during the study, while the size of the treatment responses (slopes) remained unaltered.

CONCLUSIONS Four-week treatment with rilmenidine SR 3 mg OD produced slight adaptations to drug-induced cns-effects. The reasons for these adaptations cannot be determined but may include drug tolerance and habituations to study procedures. Blood pressure control remained stable and adequate throughout the study.

Introduction

Rilmenidine (2-(dicyclopropylmethyl)-amino-2-oxazoline) is a centrally acting anti-hypertensive with binding selectivity to the I1 imidazoline receptors over α2-adrenoceptors. 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. In a study of 146 patients with hypertension (95<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).

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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 central nervous system effects (visual analogue scales and saccadic eye movements). The current study was performed after several investigations aimed at the design of an optimal slow release profile. From these studies, it was concluded that a 3 mg sustained release formulation would have the optimal profile for adequate blood pressure control with an improved side-effect profile. Since many centrally active drugs show some tolerance development to side effects during prolonged treatment, the current study aimed to investigate the effects of four-week treatment with a 3 mg sustained release formulation on the PK/PD relationships between rilmenidine plasma concentrations and central nervous system effects (saccadic eye movements and visual analogue scales).

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Methods

Design

This was a phase II single centre open non-controlled study without direct individual benefit for patients. Screening assessment took place within 17 days prior to the rilmenidine treatment. Patients were acquainted with the experimental methods and conditions in a short training session taking place within one week prior to rilmenidine treatment. Eligible patients were then withdrawn from their own anti-hypertensive treatment and switched directly into a 4-week 3 mg o.d. rilmenidine SR treatment. The withdrawal was gradual for beta-blockers, and immediate for other anti-hypertensive agents, but in all cases as short as possible in order to prevent loss of blood pressure control. Measurements for PK/PD evaluation were performed on the first day (D1-D2) of the rilmenidine treatment period and repeated after one week (D8) and four weeks (D29) of treatment. At the end of the 4-week rilmenidine treatment period, patients were re-allocated to their own anti-hypertensive treatment.

Subjects

Mild to moderately hypertensive subjects (males and females), treated with a maximum of two different anti-hypertensive drugs, gave signed informed consent to participate in this study. After a general health screen (during which relevant additional conditions were excluded, including causes for secondary hypertension) eligible patients were enrolled in the study.

Treatments

Rilmenidine Sustained Release (SR) was presented as white round-shaped film coated tablets containing 3 mg of active medication. Patients were requested to take one tablet of rilmenidine every morning under fasting conditions, with approximately 150 ml of water, 30 minutes before breakfast time. Patients were instructed to take their study medication regularly (between 07:00 and 09:00 h in the morning). Patients were instructed to maintain a diary, where intake of study medication was to be recorded.

Hæmodynamics

Blood pressures were measured after the patient had been sitting quietly for at least 10 minutes, pre-dose and repeatedly post-dose on each of the three study days. All measurements were carried out with an automated sphygmomanometer Nihon Kohden MPV 1072.

Visual Analogue Scales

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Visual analogue scales as originally described by Norris have been used previously to quantify subjective effects of benzodiazepines. From these scales, three factors can be derived as described by Bond and Lader corresponding to alertness, mood and calmness. These visual analogue scales were practiced at a training session (three times), and measured pre-dose and every hour for twelve hours after dosing, on each of the three study days.

Saccadic eye movements

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Saccadic eye movements have been used previously to quantify drug effects of rilmenidine and clonidine. Saccadic eye movements were practiced at a training session (three times), and measured pre-dose and every hour for twelve hours after dosing, on each of the three study days, with an additional measurement after 24 hours for the first dosing. Recording of eye movements was performed in a quiet room with ambient illumination. There was only one patient per session in the same room. Recording and analysis of saccadic eye movements was conducted with a microcomputer-based

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system for sampling and analysis of eye movements. The equipment used for stimulus display, signal collection and amplification was from Nihon Kohden (Nihon Kohden Corporation, Tokyo, Japan). Disposable silver-silver chloride electrodes (Medicotest N-00-s, Olstykke, Denmark) were applied on the forehead and beside the lateral canthi of both eyes of the patient for registration of the electro-oculographic signals. Skin resistance was reduced to less than 5 kOhm before application of the electrodes. Head movements were restrained using a fixed head support. The target consisted of an array of light emitting diodes on a bar, fixed at 50 cm in front of the head support. Saccadic eye movements were recorded for stimulus amplitudes of ± 15 degrees to either side. Fifteen saccades were recorded for each stimulus amplitude with interstimulus intervals varying randomly between 3 and 6

seconds. Average values of latency (i.e. reaction time), saccadic peak velocity and inaccuracy of all artifact-free saccades were used as parameters. Saccadic inaccuracy was calculated as the absolute value of the difference between the stimulus angle and the corresponding saccade, expressed as a percentage of the stimulus angle.

Blood sampling

Patients were randomly allocated to one of the following investigation schedules for pk/pd evaluation:

Days 1-2:
- Schedule 1: pre-dose and 1, 4, 7, 10 and 24 h after dosing or
- Schedule 2: pre-dose and 2, 5, 8, 11 and 24 h after dosing or
- Schedule 3: pre-dose and 3, 6, 9, 12 and 24 h after dosing.

Day 8 and Day 29
- Schedule 1: pre-dose and 1, 4, 7 and 10 h after dosing or
- Schedule 2: pre-dose and 2, 5, 8 and 11 h after dosing or
- Schedule 3: pre-dose and 3, 6, 9 and 12 h after dosing.

Blood samples for rilmenidine assay (9 ml) were obtained in lithium heparin-containing polypropylene tubes. Blood samples were drawn from an IV cannula (inserted into the arm opposite to the one where blood pressure was measured) which was kept patent using a heparin-NaCl solution. Blood samples will be taken after discarding the contents of the cannula. At the 24 hour time point on day 2, blood was collected using a vacuette with a venapuncture.

Analyses

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PHARMACOKINETICS Rilmenidine plasma levels were measured by using a gas chromatographic/mass spectrometric method. Q Rilmenidine PK was modelled using a one-compartment model with first order absorption and a lag-time using NONMEM Version V software (NONMEM Project Group, UCSF, San Francisco, CA, USA) using the first order conditional estimation method with interaction. Residual error was modelled as a combination of a constant coefficient of variation component and an additive component. Individual empirical Bayes estimates for absorption half-life, elimination half-

life, clearance and lag-time were determined for all occasions separately, and predicted individual rilmenidine concentration profiles were obtained using these estimates.

PHARMACODYNAMICS Areas under the curve were calculated for saccadic eye movement data and visual analogue scale scores using the linear trapezoidal rule on (expected) protocol times. These AUECS were subsequently divided by the corresponding time span resulting in a weighted average response. Additionally, the minimum measurement was determined with the associated actual time point for parameters with a clear response. In the case of multiple minima, the first occurrence was taken. No corrections for baseline response were implemented for either AUECS or E_{min}.

Response measurements (AUEC, E_{min}, T_{min}) were compared between the 3 days using paired Student's t-tests without correction for multiple comparisons because of the limited number (3) of contrasts and because all contrasts are sensible and clearly address the main objectives of the study.

PHARMACOKINETICS/PHARMACODYNAMICS (PK/PD) Using the predicted rilmenidine concentrations, a linear concentration-effect model with additive residual error was applied to saccadic peak velocity and VAS Alertness scores without use of an effect compartment, because individual graphs did not indicate the need for a more complex model (*eg* delay or non-linearity in the concentration-effect relationship). Parameter estimates for slopes and intercepts were obtained using NONMEM with the first order conditional estimation method. Estimates were obtained for the parameters on day 1 and changes were estimated from the day 1 value to the day 8 value and from the day 1 value to the day 29 value. Significance of changes was assessed by calculating 95% confidence intervals for the difference estimates using 2 times the reported standard error of the estimates.

Data management and additional calculations were performed using SAS for Windows V8.2 (SAS Institute, Inc., Cary, NC, USA).

Results

Subjects

Fifteen (7 male, 8 female) hypertensive patients were randomised to one of the blood sampling schedules. The age ranged from 41 to 65 years with a

mean of 51.3 (SD 7.2) years. All patients had mild to moderate essential hypertension, and received one or two anti-hypertensive agents (ACE inhibitors 33.3%, beta-blockers 26.7%, diuretics 26.7 %, angotensin II inhibitors 26.7 %, calcium antagonists 6.7 %, combined form (beta-blocker and diuretic) 6.7 % of the study population). Two patients suffered from arthrosis and these patients used allowed concomitant medication (ibuprofen 400 mg prn).

Safety assessments

No serious or severe adverse events were reported. The most frequently reported adverse events were sleepiness, dry mouth and headache, which occurred in 93%, 60% and 46.7% of the patients, respectively. Most adverse events were of a mild intensity. No clinically significant abnormalities were found for any of the safety laboratory measurements.

Pharmacokinetics

The concentration-time profile on days 1, 8 and 29 are represented in figure 1. The following population mean (approximate standard error of population mean (SEM)) pharmacokinetic parameters were estimated: elimination half life 567 min (72.0 min, inter-individual coefficient of variation (IICV) 65%), absorption half life 270 min (44.7 min, IICV 81%), clearance 0.457 L/min (0.0292, IICV 40%) and a lag time of 165 min (4.61, IICV 0%).

Hæmodynamics

After patients switched rapidly from their own antihypertensive treatment(s) to rilmenidine. The mean (SD) pre-dose blood pressures on day 1 were 131.7/76.6 (SD 12.1/7.9) mmHg. On day 29, the average (SD) pre-dose systolic/diastolic blood pressure was 140.5/80.6 (SD 21.0/10.3) mmHg.

Saccadic eye movements

The effects of prolonged treatment on the AUECS of saccadic peak velocity (SPV), reaction time (RT) and inaccuracy are presented in Table 1. The average curves for saccadic peak velocity (SPV) on days 1, 8 and 29 are presented in

Figure 2. The primary endpoint of saccadic peak velocity (SPV AUEC) showed no significant changes during four weeks of treatment with rilmenidine SR 3.0 mg OD. The minimum SPV values during days 1, 8 and 29 of treatment were comparable, with average (SD) values of 413.2 (48.2), 415.4 (53.7) and 401.5 (63.0) deg/sec, respectively. Hence, these data provide no indications for tolerance development. There are clear indications for a treatment effect that is comparable among the three treatment days. The average minimum values (E_{min}) on the three treatment days all represent decreases in excess of 15%, which is well over the level of clinical significance of 10% below baseline, associated with a decrease in SPV observed after the loss of one night of sleep. The other two parameters (reaction time and inaccuracy) did not show any significant effects except for a decrease in AUEC inaccuracy for day 8 compared to day 1.

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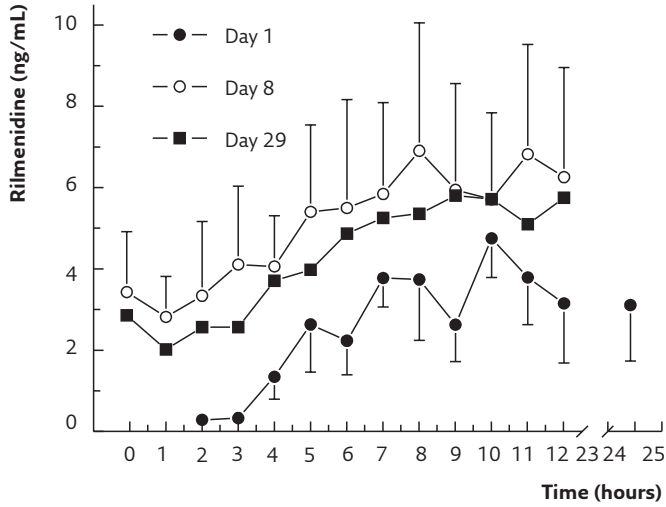
FIGURE 1 **Average rilmenidine concentration-time profiles at day 1, 8 and 29 (mean + SD)**



Visual analogue scales

The AUECS of VAS alertness, mood and calmness are represented in Table 1. The average curves for visual analogue scale alertness on days 1, 8 and 29 are presented in Figure 3. All subjective scales showed significant increases from day 1 to day 8 and from day 1 to day 29. No significant changes were observed from day 8 to day 29. The VAS baseline values all increased from day 1 to day 8 and from day 1 to day 29.

TABLE 1 **Time-corrected AUECS (0-12 h) for all pharmacodynamic parameters: Mean, standard deviations (SD) and contrasts with 95% confidence intervals (95% CI) between treatment days (* p<0.05)**

	Day 1 Mean (SD)	Day 8 Mean (SD)	Day 29 Mean (SD)	Day 1 - 8 Mean (95% CI)	Day 1 - 29 Mean (95% CI)	Day 8 - 29 Mean (95% CI)
Saccadic peak velocity (deg/sec)	458.9 (41.7)	458.9 (44.4)	456.5 (48.1)	0.0 (-12.1, 12.1)	2.4 (-17.1, 21.9)	2.4 (-13.6, 18.4)
Saccadic reaction time (msec)	236 (21)	229 (21)	231 (22)	7.1 (-0.5, 14.7)	4.7 (-3.7, 13.1)	-2.4 (-9.0, 4.2)
Saccadic inaccuracy (%)	9.46 (3.19)	8.39 (2.62)	8.56 (2.86)	1.06 (0.38, 1.75) *	0.89 (0.10, 1.69) *	-0.17 (-0.65, 0.31)
VAS alertness (mm)	72.1 (13.5)	77.4 (12.6)	78.1 (12.7)	-5.36 (-8.16, -2.56) *	-6.04 (-9.18,-2.89)*	-0.68 (-3.43, 2.08)
VAS mood (mm)	78.9 (12.0)	81.4 (10.9)	82.4 (11.7)	-2.45 (-4.23, -0.66) *	-3.52 (-5.60,-1.44)*	-1.07 (-2.82, 0.68)
VAS calmness (mm)	79.9 (7.6)	83.9 (7.4)	84.5 (6.9)	-3.95 (-5.92, -1.99) *	-4.61 (-7.25,-1.96)*	-0.65 (-2.69, 1.39)

Pharmacokinetics/pharmacodynamics (PK/PD)

PK/PD parameter estimations for VAS alertness and SPV are represented in table 2. The average PK/PD relationships are presented in figure 4 for SPV and figure 5 for VAS alertness. Both parameters (VAS and SPV) showed linear concentration-effect relationships. No significant changes in slopes between days were observed for VAS or SPV, indicating that the CNS-effect of rilmenidine per unit concentration remained unaltered. The intercept for the SPV PK/PD relationships did not change significantly from day 1 to either day 8 or day 29. The intercept of the VAS alertness scale increased significantly after day 1: the difference between day 8 and day 1 was 12.5 (4.5, 20.5) mm and the difference between day 29 and day 1 was 13.0 (2.9, 23.1) mm.

Discussion

This study was part of a series of investigations, designed for the development of an optimal controlled release formulation of the centrally active antihypertensive agent rilmenidine. Previous studies showed clear concentration dependent effects on blood pressure and the central nervous system of a potential sustained release profile of rilmenidine. Furthermore, these studies suggested that the optimal therapeutic window would be

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FIGURE 2 **Average saccadic peak velocity-time profiles at day 1, 8 and 29**

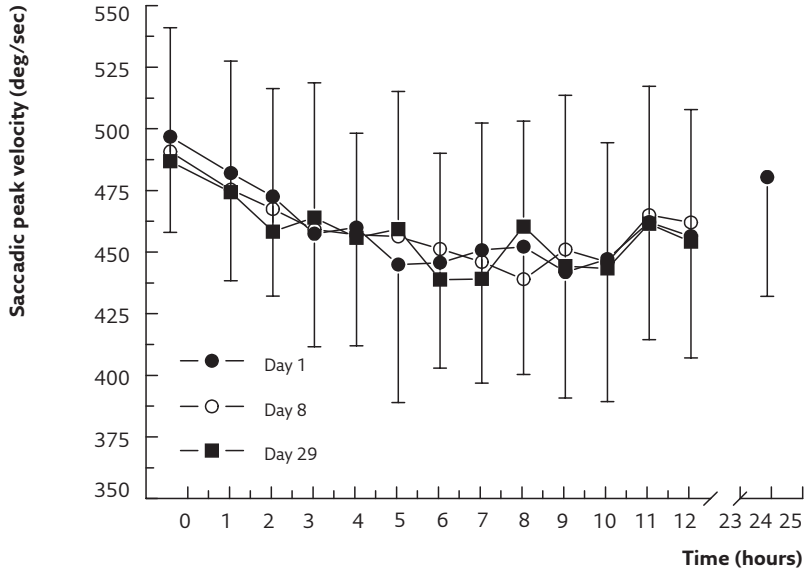

FIGURE 3 **Average visual analogue scale alertness-time profiles at day 1, 8 and 29**

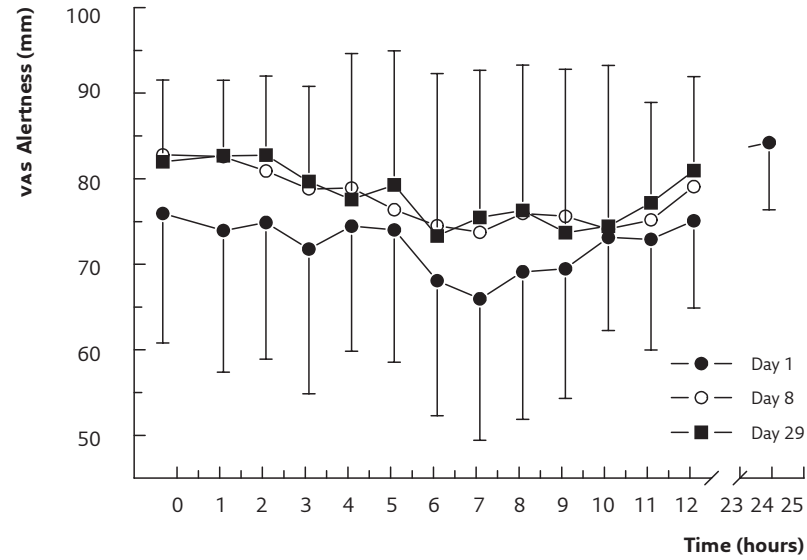

TABLE 2 **PK/PD parameters using empirical Bayes estimates for saccadic peak velocity and VAS alertness. Population average, standard error of the population average (Mean), 95% confidence intervals (95% CI) and inter-individual variability as standard deviation (IISD)**

	Mean	SEM	95% CI	IISD
Saccadic peak velocity				
Slope day 1 (deg.sec-1.ng-1.mL)	-6.66	1.63	-9.9 / -3.4	4.77
Change to day 8	-0.0870	2.35	-4.9 / 4.6	
Change to day 29	-0.286	2.96	-6.2 / 5.6	
Intercept day 1 (deg.sec-1)	476	9.69	457 / 495	37.5
Change to day 8	16.2	12.6	-9.0 / 41.4	
Change to day 29	9.34	18.4	-27.5 / 46.1	
Residual variability (SD)	26.1			
VAS alertness				
Slope day 1 (mm.ng-1.mL)	-0.828	0.519	-1.9 / 0.2	2.06
Change to day 8	-1.37	1.00	-3.4 / 0.6	
Change to day 29	-1.32	1.08	-3.5 / 0.8	
Intercept day 1 (mm)	75.5	3.47	68.6 / 82.4	9.42
Change to day 8	12.5	4.02	4.5 / 20.5	
Change to day 29	13.0	5.06	2.9 / 23.1	
Residual variability (SD)	7.17			

would be 4-6 ng/ml. Although effective, these concentrations have shown to produce some changes in saccadic eye movements and visual analogue scales effects, which could be consistent with the clinical phenomenon of sedation. These effects could become less pronounced during prolonged treatment, due to tolerance development. The aim of this study was to evaluate potential changes in pharmacokinetic/pharmacodynamic (PK/PD)-relationships for these central nervous system effects during a 4-week treatment period with rilmenidine SR 3 mg OD.

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The design of the study was based on two assumptions. First, a rapid switch from prestudy antihypertensives to rilmenidine was considered unlikely to affect the central nervous system effects. A rapid switch could affect the blood pressure control, which soon after the switch would still be partly affected by the interrupted prestudy treatment and would not be individually optimised. However, adequate long-term blood pressure control has already been established with rilmenidine, and this was not the aim of the study. The second assumption was that PK/PD-analyses reduce the need for a placebo-control. Any major placebo-response would dilute the relationship

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FIGURE 4 **Average PK/PD relationship between predicted rilmenidine concentrations and saccadic peak velocity**

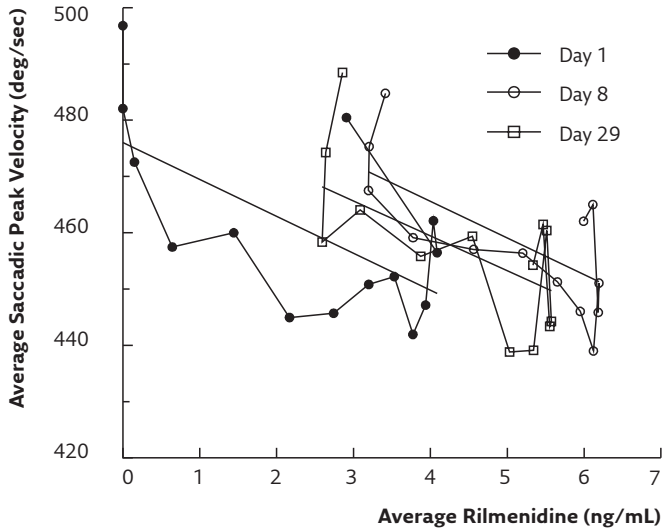
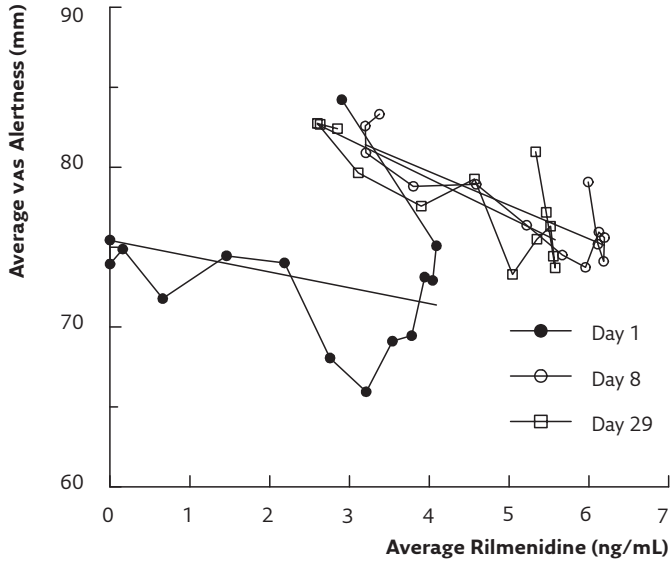


FIGURE 5 **Average PK/PD relationship between predicted rilmenidine concentrations and VAS alertness**



between the drug concentration and the pharmacodynamic parameter. Hence, a clear concentration-effect-relationship was considered a strong argument for drug-dependency of the parameter.

PK/PD-analyses were essential for the aims of the study, because they can be used to quantify changes in sensitivity to the drug and the development of tolerance. For linear concentration-effect-relationships, changes can occur in the slope and/or the intercept of the concentration-effect-curve. A decreased slope signifies that the same concentration range produces a less pronounced response. In this case, the effect at the highest observed concentration is decreased, for instance, due to desensitisation or dynamic counter-regulation. An increase in the intercept signifies that the entire concentration-effect-curve is right-shifted. Elevated pre-dose values will usually lead to an increased intercept of the concentration-effect curve.

The accumulation of rilmenidine during the four week period did not lead to an increase in CNS-effects. This was due to shifts in the concentration-effect-relationships for SPV and VAS Alertness scores. There were no changes in the slopes of the PK/PD-relationships from day 1 to day 8 or 29, whereas the intercept tended to increase. This net effect of these changes was that subjects became less sensitive to rilmenidine's SPV-effects. This finding was corroborated by the subjective measures of sedation. The AUEC of the visual analogue scales (VAS) for alertness increased on days 8 and 29 compared to day 1. These elevated AUECS could be largely attributed to an increase in predose alertness. The treatment responses remained unchanged, with rising rilmenidine concentrations. As a result, the PK/PD-relationship with VAS alertness showed a similar pattern as the PK/PD-relationship with SPV: slopes remained unaffected during multiple dosing, while intercepts increased. Compared to day 1, VAS alertness increased statistically significantly on both day 8 and 29.

The mechanisms behind these changes are unclear. The main PK/PD-changes for VAS and SPV are increases in the intercepts of the concentration-effect relations. Thus, a higher concentration range produces a similar treatment effect. Adaptation phenomena can cause an increased pre-dose effect (*eg* rebound after drug withdrawal), but this has not been reported for rilmenidine, and is particularly unlikely considering the accumulation of the drug with this sustained release profile. Pharmacological tolerance to the central nervous system effects of rilmenidine would primarily (or at least additionally) be expected to cause reductions in slopes of the concentration-effect relations, which were not observed in this study.

Therefore, explanations for the observed alterations do not seem to be purely pharmacological. In addition, methodological causes can be considered, related to learning effects or habituation to the study procedures. If causes for the adaptations would be methodological, this would also be expected in a placebo group. However, a recent four-week placebo-controlled trial with the imidazoline antihypertensive moxonidine did not reveal any changes in the placebo-treated group. The concentration-effect-relationships in the moxonidine-group displayed clear changes in intercepts but not in slopes - quite comparable to the findings of the current study. Although the reasons for these habituation processes cannot be determined exactly, it is clear that the subjective predose assessment of alertness (and mood and calmness) improved slightly during the study, while adequate blood pressure control was observed throughout the four-week treatment period.

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