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Influence of the dosing interval on prolactin release after remoxipride

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1 The prolactin response following administration of the D_2-dopamine receptor antagonist remoxipride was studied in eight healthy male volunteers. The purpose of the study was to investigate the duration of a refractory period of prolactin release following two doses of remoxipride. A further aim was to compare the prolactin response following remoxipride and thyrotropin release hormone (TRH) during the refractory period. The subjects received two 30 min intravenous (i.v.) infusions of remoxipride 50 mg with different time intervals between the two doses, in a randomized six period crossover design. The time intervals between the two remoxipride doses were 2, 8, 12, 24 and 48 h. On one occasion the remoxipride dose was followed by an i.v. injection of TRH after 2 h.

2 The plasma peak prolactin concentrations obtained after the first remoxipride dose correspond to a maximal release of prolactin according to earlier studies. A small second peak of prolactin was observed after 2 h. The release was gradually increased with longer time intervals between the consecutive doses. The refractory period for a second prolactin release similar to the first one after remoxipride was found to be 24 h for most of the subjects.

3 TRH resulted in a faster and higher increase in prolactin response of a shorter duration than after remoxipride administered 2 h after the first dose.

Keywords prolactin neuroleptics remoxipride man pharmacokinetics tolerance refractoriness

Introduction

Antipsychotic drugs (neuroleptics) are believed to exert their clinical effect by interacting with dopamine receptors in the brain. These substances increase prolactin secretion into the blood by preventing the inhibitory effect of dopamine on D_2-dopamine receptors in the anterior pituitary [1, 2]. Prolactin secretion contributes to some of the unwanted effects of neuroleptics such as menstrual disturbances, amenorrhea, galactorrhea, gynecomastia and impotence, probably associated with the effects on the hypothalamic-pituitary-gonadal axis.

Remoxipride, [(-)(S)-3-bromo-*N*-(1-ethyl-2-pyrrolidinyl)-methyl]-2,6-dimethoxy benzamide, is a new antipsychotic of the benzamide type. It is a selective D_2-dopamine receptor antagonist [3]. Controlled clinical trials have shown that remoxipride has a good antipsychotic effect, with a significantly lower frequency of extrapyramidal symptoms compared with haloperidol [4, 5]. The effect of remoxipride on plasma prolactin elevation is short-lasting [6, 7]. The trough plasma prolactin levels during steady-state treatment are generally not elevated, or only mildly to moderately elevated above the normal levels, during treatment with remoxipride, which differentiates remoxipride from classical neuroleptics [8–11].

Findings during repeated administration of remoxipride to patients, where the prolactin response with regard to peak plasma prolactin concentrations diminished, led us to be interested in prolactin responsiveness in relation to dosing intervals [12–14]. Results on prolactin release from the literature regarding administration of other neuroleptics (sulpiride,

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haloperidol) and TRH have suggested a refractory period of prolactin response [15–17]. The refractory period was seen as lack of prolactin increase or a grossly blunted increase after a 24 h dosing interval of sulpiride in man [15, 16]. However, when the interval between the two sulpiride injections was 48 h, both administrations caused a sharp increase in prolactin [15]. In rats, sulpiride induced a 'refractory' period of prolactin response of 24 h with no response after 2 h following sulpiride or haloperidol [17].

Unresponsiveness of prolactin was reported when a neuroleptic (sulpiride or domperidone) or TRH was administered in man as a bolus injection at the end of an i.v. infusion of the same substance [18, 19]. However, a TRH injection at the end of the neuroleptic infusion resulted in an increase in prolactin concentrations. Similarly a neuroleptic injection obtained a peak at the end of a TRH infusion. Administration of TRH and domperidone injections concomitantly resulted in additive prolactin increase [18]. These results indicate that different mechanisms are involved in the release of prolactin after TRH and neuroleptics such as sulpiride and domperidone.

The peak plasma prolactin levels ($C_{max,PRL}$) have been reported to be dose-related up to a maximal release following administration of remoxipride [13, 14, 29], sulpiride [16, 21–25] and also following TRH [26, 27]. Maximal prolactin peak concentrations are expected to be achieved with the doses of remoxipride and TRH administered in the present study [26, 27].

The prolactin response following remoxipride was studied from a pharmacokinetic and clinical pharmacological perspective. The purpose of this study was to investigate if there is a 'refractory period' for prolactin release following remoxipride and if so, to measure the duration of that period. A further objective was to compare the release of prolactin after remoxipride and TRH.

Methods

Subjects

Eight healthy male volunteers between the ages of 29 and 45 years (mean 36 ± 6 years) participated in the study. They were non-smoking and healthy according to medical history, physical examination, ECG and laboratory tests. All subjects had normal TSH values and all were rapid hydroxylators of debrisoquine [28] (Table 1).

The study was approved by the local Ethics Committee at Södersjukhuset, Stockholm and was performed according to the Declaration of Helsinki. Each volunteer gave their signed informed consent to participate.

Study design

The study was performed according to a randomised six period cross-over design. Each subject participated in six treatment sessions on six separate occasions with at least weekly intervals between them. On five occasions two repeated single doses of remoxipride 50 mg were administered as intravenous infusions during 30 min with varying time intervals between them. The second dose was administered 2, 8, 12, 24 or 48 h after the first dose. On one of the six occasions the first remoxipride dose was followed by an intravenous injection over 2 min of TRH 0.2 mg administered 2 h after remoxipride.

Subjects were allocated randomly to sequences of the following time intervals, with the following abbreviations:

0 h remoxipride and 2 h remoxipride (R-R2 and R2)
0 h remoxipride and 8 h remoxipride (R-R8 and R8)
0 h remoxipride and 12 h remoxipride (R-R12 and R12)
0 h remoxipride and 24 h remoxipride (R-R24 and R24)
0 h remoxipride and 48 h remoxipride (R-R48 and R48)
0 h remoxipride and 2 h TRH (R-T2 and T2)

i.e. R-R2 refers to the first dose administered and R2 to the second dose etc.

All i.v. infusions were started at 08.00 or 09.00 h. Two Venflon® i.v. cannulas were inserted into the forearm veins, one in each arm. The infusion was administered in one arm and the samples were taken from the other. All infusions were administered intravenously at 5 ml min^{-1} (1.68 mg min^{-1}) over exactly 30 min, using an infusion pump (IMED 960 volume pump). The subjects were recumbent during the infusions and injections and the first sampling hours thereafter.

No other drugs or alcohol were allowed during 48 h prior to or during each experimental session. Caffeine containing beverages (coffee, tea, coca cola) were not allowed during the first 6 h on Day 1 of the experimental sessions. The subjects were instructed not to engage in any strenuous or athletic activities during the days of drug administration and to remain at the study site for the first 4 h after each administration.

Study drugs

Stock solutions of remoxipride hydrochloride monohydrate salt 5 mg ml^{-1} were produced at Astra Arcus AB, Södertälje, Sweden. The solutions for infusion (0.336 mg ml^{-1}) were prepared immediately before use by adding physiological saline to the stock solution. The TRH® solution 0.1 mg ml^{-1} for injection was produced by Roche.

Blood sampling

Over the first 4 h after each dose blood samples were taken using the 'heparin-lock' technique from an indwelling catheter, thereafter Venoject® tubes were used. Plasma was separated by centrifugation within 1 h and transferred to polypropylene tubes (Nunc® tubes). The samples were stored at −20° C until analysed.

Specimens were drawn just prior to dosing and according to the following schedule: 10, 15, 20, 30, 40, 50, 60, 90 min, 2, 4, 8, 12 and 24 h for all treatments in the second administration. However, during the first administration the schedule was only followed up to the start of the second administration.

Adverse events

Adverse events spontaneously reported by the subject or observed by the staff were recorded, specifying the onset, severity and duration of each symptom. In addition, open questioning regarding adverse symptoms was performed before and at the end of each experimental occasion. A general question such as 'Have you experienced something out of the ordinary?' was asked. Any symptoms reported were evaluated further.

Analytical procedures

Plasma concentrations of remoxipride were determined by reversed phase h.p.l.c. at the Department of Bioanalysis at Astra Arcus AB, Södertälje [29]. The limit of determination was 0.05 μmol l^{-1} in plasma. The interassay precision (CV) for spiked control samples was 1.8% at 0.2 μmol l^{-1} and 3.2% at 5 μmol l^{-1}. The intra-assay precision at 0.2 μmol l^{-1} was 1%.

Prolactin concentrations in plasma were determined by a commercial radioimmunoassay kit (Diagnostic Prod Corporation, Los Angeles, California) at the Unit for Applied Biochemistry, Huddinge University Hospital, Sweden. The determination limit was 5 μg l^{-1} (0.22 nmol l^{-1}). The interassay coefficient of variation was below 14% during all assays, covering the concentration interval between 10 and 80 μg l^{-1}. The intra-assay coefficient of variation never exceeded 8%. The normal values in males are below 20 μg l^{-1}. All samples from one subject were analysed during the same day.

Pharmacokinetic calculations

Pharmacokinetic parameters of remoxipride were calculated according to standard noncompartmental methods for each individual and each administration [30]. The area under the remoxipride plasma concentration *vs* time curve (AUC) was calculated using the logarithmic trapezoidal rule for decreasing concentrations. Extrapolation to infinity was made by adding the calculated concentration at the last sampling time divided by the slope of the log terminal elimination phase.

For prolactin, the maximum plasma concentration ($C_{max,\ PRL}$) and the time to the peak concentration ($t_{max,\ PRL}$) were observed for each subject after each administration. The area under prolactin concentration *vs* time curve ($AUC(0,24)_{PRL}$) was estimated using the linear trapezoidal rule. For the first doses and for the second dose administered after 48 h $\Delta C_{max,PRL}$ and $\Delta AUC(0,24)_{PRL}$ were calculated as the C_{max} and AUC above baseline prolactin levels for each treatment. Whereas, for the second dose they were calculated as the difference between individual $C_{max,PRL}$ or $AUC(0,24)_{PRL}$ for each second treatment and the prolactin concentrations or $AUC(0,24)_{PRL}$ for the reference (the first dose followed by a second dose after 48 h) at the corresponding time points.

Statistical analysis

The RS1 [31, 32] and SAS® [33, 34] were used for the statistical analyses. Statistical analyses were performed on all available pharmacokinetic data which included all subjects who received their study medication and had at least one observation recorded in each period while on study medication. Pairwise differences between respective measurements for the prolactin plasma concentration data were assessed using the Wilcoxon Rank Sum Test [35]. Adjustments for multiplicity were not made. Period effects were assessed using analysis of variance models (ANOVA) [36]. All statistical tests were two-sided and statistical significance was declared if the P value was ≤ 0.050.

Results

Drug plasma concentrations

The basic pharmacokinetic parameters were estimated with mean (± s.d.) values for CL, V and V_{ss} of 106 ± 17 ml min^{-1}, 44 ± 6.1 l and 39 ± 6.1 l, respectively. The AUC, $t_{1/2}$ and C_{max} values were 19.2 ± 3.1 μmol l^{-1} h, 5.16 ± 1.17 h and 3.64 ± 0.56 μmol l^{-1}, respectively (Table 1). The interindividual variability was two-fold or less in CL, V_{ss}, V, AUC, $t_{1/2}$ as well as C_{max}. The intraindividual variability was less than 1.5-fold in CL, V_{ss}, V, AUC, $t_{1/2}$ and C_{max}.

Prolactin plasma concentrations

A transient increase in plasma prolactin concentrations was seen after all remoxipride and TRH administrations (Figure 1). The prolactin levels increased within 10 min after start of the first infusions (Figure 1). The peak prolactin level (mean ± s.d.) following the first doses of remoxipride was 56 ± 15 (range 37–73) μg l^{-1}, and was reached after 0.78 ± 0.17 (0.58–1.04) h (Table 2). The t_{max} of prolactin occurred later than the t_{max} of remoxipride, which was 0.51 ± 0.04 (0.48–0.60) h. $t_{max,PRL}$ following the first and second doses was similar (NS). Some of the individual plasma prolactin *vs* time curves show secondary peaks or one peak followed by an inflexion. The $AUC(0,24)_{PRL}$ was 356 ± 74 μg l^{-1} h.

The prolactin increase ($\Delta C_{max,PRL}$) following the second remoxipride dose increased with increasing time intervals between the doses (Figure 2 and Table 3). A similar prolactin response to that after the first dose with regard to $\Delta C_{max,PRL}$ was reached after 24 h in five subjects and after 48 h in three subjects. For the dosing intervals shorter than 24 h (R2, T2, R8 and R12) the $\Delta C_{max,PRL}$ response was statistically significantly less than after the first dose of rem-

Table 1 Individual pharmacokinetic parameters of remoxipride (mean ± s.d.) following 30 min intravenous infusions of 50 mg in eight healthy male subjects

Subject	*Body weight (kg)*	*Debrisoquine ratio*	C_{max} *(μmol l^{-1})*	t_{max} *(h)*	*AUC (μmol l^{-1} h)*	$t_{1/2}$ *(h)*	*CL (ml min^{-1})*	V *(l)*	V_{ss} *(l)*
1	78	0.88	3.02 ± 0.54	0.50	16.8 ± 2.3	5.27 ± 0.74	118 ± 17	51 ± 7	48 ± 5
2	84	0.75	4.11 ± 0.28	0.50	15.1 ± 0.5	4.07 ± 0.27	131 ± 4	44 ± 2	40 ± 2
3	74	0.89	3.49 ± 0.40	0.50	19.9 ± 3.4	5.26 ± 0.62	101 ± 16	45 ± 9	41 ± 5
4	85	0.36	4.32 ± 0.43	0.50	18.7 ± 2.8	4.72 ± 1.10	106 ± 14	39 ± 6	33 ± 4
5	81	0.24	3.62 ± 0.53	0.50	16.5 ± 2.5	3.55 ± 0.58	121 ± 18	35 ± 5	33 ± 5
6	81	6.8	2.93 ± 0.51	0.60 ± 0.38	23.3 ± 3.7	7.40 ± 1.41	86 ± 16	51 ± 3	47 ± 3
7	91	1.03	3.31 ± 0.22	0.50	19.4 ± 1.1	5.08 ± 0.56	102 ± 6	43 ± 5	38 ± 2
8	77	0.56	4.35 ± 0.52	0.48 ± 0.06	23.7 ± 2.9	5.96 ± 1.02	84 ± 11	41 ± 9	35 ± 5
Mean†	81		3.64	0.51	19.2	5.16	106	44	39
s.d.†	5		0.56	0.04	3.1	1.17	17	6	6
Min†	74		2.92	0.48	15.1	3.55	84	35	33
Max†	91		4.35	0.60	23.7	7.40	131	51	48
*n**			(8)[a]	(8)[a]	(7)[b]	(10)[c]	(7)[b]	(7)[b]	(7)[b]

†Calculated from the individual mean values.
**n* (number of treatments) used in the calculations of mean values.
[a]Treatments used in the calculations R-R2, R-R8, R-R12, R-R24, R-R48, R-T2, R24, R48.
[b] R-R8, R-R12, R-R24, R-R48, R-T2, R24, R48.
[c] R-R8, R-R12, R-R24, R-R48, R-T2, R2, R8, R12, R24, R48.

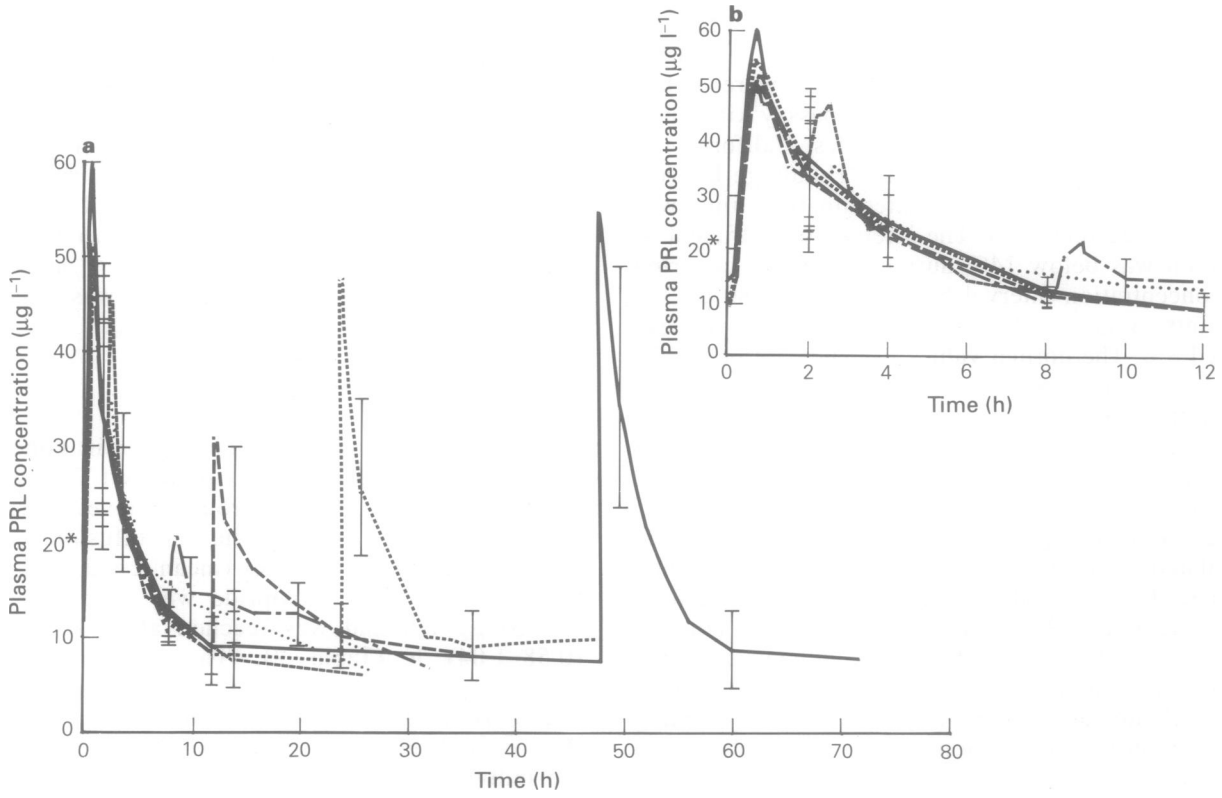

Figure 1 (a–b) Mean plasma prolactin concentrations (± s.d.) following two i.v. drug administrations (remoxipride and/or TRH) at different time intervals in eight healthy male subjects. ..... R-R2 and R2, – – – R-R8 and R8, ———— R-R12 and R12, ····· R-R24 and R24, ——— R-R48 and R48, – – – – – – R-T2 and T2. *Upper normal limit for male subjects.

oxipride. With regard to $\Delta AUC(0,24)_{PRL}$ similar values to the first dose were obtained after 12 h in one subject, 24 h in four subjects and after 48 h in the remaining three subjects. $\Delta AUC(0,24)_{PRL}$ was statistically significantly lower for R2, T2, and R8 as compared with the first dose.

Administration of a bolus injection of TRH 0.2 mg as the second dose 2 h after remoxipride gave a

Table 2 Individual pharmacokinetic parameters of prolactin (mean ± s.d.) following the first intravenous infusions of remoxipride 50 mg during 30 min in eight healthy male subjects

Subject	$C_{max,PRL}$ ($\mu g\ l^{-1}$)	$t_{max,PRL}$ (*h*)	$AUC(0,24)_{PRL}$ ($\mu g\ l^{-1}\ h$)	$\Delta C_{max,PRL}$ ($\mu g\ l^{-1}$)	$\Delta AUC(0,24)_{PRL}$ ($\mu g\ l^{-1}\ h$)
1	52.0 ± 4.7	0.75 ± 0.09	300.6 ± 48.4	42.4 ± 3.1	110.4 ± 33.9
2	38.2 ± 2.0	0.58 ± 0.09	271.6 ± 23.8	29.1 ± 2.9	59.8 ± 33.1
3	69.0 ± 8.3	1.04 ± 0.60	420.1 ± 64.9	61.6 ± 9.5	270.7 ± 69.2
4	46.9 ± 3.9	0.61 ± 0.09	289.9 ± 31.4	37.6 ± 4.2	89.5 ± 16.1
5	72.6 ± 9.8	0.78 ± 0.80	403.4 ± 0.7	56.5 ± 11.1	111.2 ± 6.9
6	58.2 ± 9.8	0.69 ± 0.16	471.6 ± 28.2	47.8 ± 10.3	225.0 ± 3.2
7	36.9 ± 3.5	0.75 ± 0.09	301.0 ± 2.8	29.0 ± 4.2	97.0 ± 41.3
8	72.6 ± 3.0	1.03 ± 0.73	391.8 ± 37.2	58.5 ± 10.9	223.2 ± 31.5
Mean†	55.8	0.78	356.2	45.3	148.4
s.d.†	14.7	0.17	74.2	12.9	78.6
Min†	36.9	0.58	271.6	29.0	59.8
Max†	72.6	1.04	471.6	61.6	270.7
*n**	(6)[a]	(6)[a]	(2)[b]	(6)[a]	(2)[b]

†Calculated from the individual mean values.
**n* (number of treatments) used in the calculations of mean values.
[a]Treatments used in the calculations: R-R2, R-R8, R-R12, R-R24, R-R48, R-T2.
[b]R-R24, R-R48.

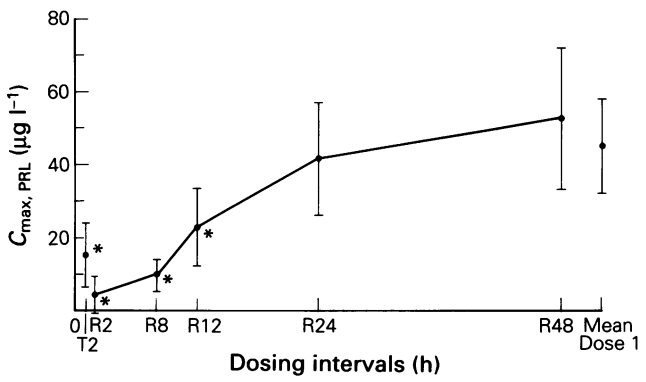

Figure 2 The $\Delta C_{max,PRL}$ following the second remoxipride dose (or TRH) administered at different time intervals after the first dose in eight healthy male subjects (mean ± s.d.). *Statistically significant differences *vs* dose 1 ($P < 0.05$).

higher peak prolactin concentration in all subjects compared with a second remoxipride administration after 2 h (R2) (Figure 1). The $t_{max,PRL}$ following TRH was statistically significantly shorter than following remoxipride. The ΔAUC(0,24) was lower for TRH than remoxipride both administered after 2 h in all subjects but one. After TRH the prolactin levels returned to baseline values earlier than after remoxipride (R2). The prolactin levels had returned to baseline values within 17 ± 9 h (range 4–48 h) after the second doses of remoxipride and within 12 ± 8 h (range 4–24 h) after TRH.

Adverse events

All adverse events reported were of mild severity. Following remoxipride treatment inner restlessness was reported by one subject at each session (also after TRH), motor restlessness once by two subjects, tiredness and drowsiness once by two subjects and one subject reported that he was feeling high. Prickling sensation in mouth was reported by one subject at two sessions, one after remoxipride and one after TRH. After the TRH injection flushing was reported by three subjects, sensation of warmth by one, sweating by two, micturition urgency by one, and nausea by one subject.

Discussion

The pharmacokinetics of remoxipride showed a low inter- and intraindividual variability. The pharmacokinetic parameters of remoxipride (CL, V and V_{ss}) from the present study confirm those previously reported [37, 20]. Remoxipride is a pure enantiomer which is eliminated both by metabolism (~75%) and renal excretion of unchanged drug (~25%). No active metabolites have been reported in man [38]. It is a low clearance drug with a plasma clearance of 106 ± 17 ml min^{-1}, and with a bioavailability above 90%.

The prolactin peak concentrations obtained in the present study following the first doses of remoxipride are in the same magnitude as those previously suggested to represent a maximal release [7, 13, 20, 37]. The $C_{max,PRL}$, $AUC(0,24)_{PRL}$ and $t_{max,PRL}$ were similar to those reported following i.v. infusions of 50 mg remoxipride and following single doses of 70, 100 and 140 mg remoxipride given as oral rapid administrations such as solution, immediate release capsules or intramuscular injection [7, 13, 20, 37].

The plasma prolactin concentration following the i.v. infusions of remoxipride increased rapidly within 10 min and the peak was reached at 30–60 min. A rapid rise and a short t_{max} of prolactin has been suggested to indicate a direct action on the receptors on the lactotrophs in the pituitary by TRH [26, 27, 39] and sulpiride [15, 24].

Table 3 Pharmacokinetic parameters of prolactin (mean ± s.d.) following the second intravenous administration of remoxipride 50 mg or TRH 0.2 mg in eight healthy male subjects

Dose 2	$\Delta C_{max,PRL}$ ($\mu g\ l^{-1}$)	$t_{max,PRL}$ (*h*)	$\Delta AUC(0,24)_{PRL}$ ($\mu g\ l^{-1}\ h$)
R2	4.4 ± 5.1	0.49 ± 0.26	27.7 ± 26.7
R8	9.9 ± 4.5	0.77 ± 0.15	64.8 ± 39.1
R12	23.1 ± 10.5	0.69 ± 0.11	94.8 ± 43.3
R24	41.7 ± 15.4	0.79 ± 0.15	132.2 ± 73.1
R48	52.9 ± 19.4	0.71 ± 0.15	160.5 ± 93.3
T2	15.6 ± 8.8	0.41 ± 0.22	−32.9 ± 38.2
Mean of dose 1†	45.3 ± 13.0[g]	0.72 ± 0.08[g]	148.3 ± 78.6[h]
Statistics	$P < 0.001$[a,b,f]	$P \leq 0.005$[f]	$P \leq 0.001$[a,f]
P value	$P \leq 0.01$[c], NS[d–e]	NS[a–e]	$P < 0.05$[b], NS[c–e]

†Calculated from the individual mean values.
[g]Treatments used in the calculations R-R2, R-R8, R-R12, R-R24, R-R48, R-T2.
[h]R-R24, R-R48.
Comparisons: [a]Dose 1-R2, [b]Dose 1-R8, [c]Dose 1-R12, [d]Dose 1-R24, [e]Dose 1-R48, [f]Dose 1-T2.
NS = Non significant, i.e. $P > 0.05$.

After administration of remoxipride a slower decrease in prolactin levels was observed than what would be explained by the reported prolactin half-life *per se* (10–30 min) [40–42]. It was also slower than after administration of TRH. The slower decrease was observed as a second peak or as an inflexion on the prolactin concentration-time curves after remoxipride. Pharmacokinetically the inflexion indicates a second process in the release of prolactin. This might suggest either a release from less easily releasable prolactin pools, or a release of newly synthesised prolactin. It could also be an effect of feedback systems or an effect on hypothalamic dopamine added to the direct effect on the pituitary. Furthermore, it could be related to the pharmacokinetics of a possible unknown metabolite of remoxipride.

A small release of prolactin (about 15% based on $\Delta C_{max,PRL}$) was observed following the second remoxipride dose 2 h after the first one. The release was gradually increased with longer time intervals between the two consecutive remoxipride doses. After an interval of 24 or 48 h the second release was similar to the first one. The time dependent unresponsiveness in plasma prolactin levels after the second dose is most likely due to a limited amount of prolactin in easily releasable pools, which takes 24 to 48 h to restore. Another explanation might be that the D_2-dopamine receptors have a changed sensitivity for a time period, and that it takes 24 to 48 h to reoccupy these receptors. A feedback system, which in some other way turns off the release is another theoretical possibility. The refractoriness observed after remoxipride could also be referred to as development of acute tolerance.

A time interval of 2 h following sulpiride or haloperidol resulted in no observable prolactin response in plasma levels at all [15, 17]. After sulpiride the prolactin cells in man were almost unresponsive to a second injection for more than 24 h [15]. After a dosing interval of 48 h the second sulpiride dose resulted in a prolactin peak, although it was lower than that after the first dose. Remoxipride has a shorter 'refractory period' for prolactin release than sulpiride, since a small peak was seen already after a dosing interval of 2 h and a peak prolactin concentration similar to that after the first dose was reached again after 24 h in most subjects. Remoxipride and sulpiride may have different effects on prolactin turnover after the initial increase in plasma prolactin concentrations. The duration of increased prolactin concentrations from baseline levels has also been reported to be shorter for remoxipride than for sulpiride [7]. The trough levels of prolactin were markedly increased following repeated administrations of sulpiride in psychiatric patients [43]. During treatment with remoxipride the trough prolactin levels were not increased or only mildly or moderately increased [8–11].

The plasma prolactin response following a TRH injection has been reported to be more rapid and of shorter duration than following neuroleptics such as a haloperidol injection and sulpiride administered i.m. [24, 44]. In our study the prolactin response following an injection of TRH was different from that following a 30 min infusion of remoxipride. It was observed that the ΔAUC of prolactin following TRH was smaller than that following remoxipride, even though the $\Delta C_{max,PRL}$ was higher and the $t_{max,PRL}$ was shorter. The longer lasting effect on prolactin after remoxipride in contrast to TRH might be connected to their different pharmacokinetics. TRH has a short elimination half-life of about 7 min as compared with the remoxipride half-life of about 5 h [37, 45]. The two substances were also administered differently, TRH as a bolus injection over 2 min in similarity to other studies, and remoxipride as a 30 min i.v.

infusion. It is therefore not possible to differentiate clearly the effects of the administration rate from the mechanisms.

The diminished response of prolactin is most likely related to a depletion of the stored prolactin in pools responsive to remoxipride. The observed refractory period in prolactin response after remoxipride is most likely an explanation of the observation of lower peak prolactin concentrations after repeated dosing three times or twice daily [12, 13]. The comparatively short refractory period of about 24 h for remoxipride might also explain the shorter duration of elevated prolactin levels [6, 7] and the less elevated trough prolactin levels reported in patients during treatment with remoxipride compared with other neuroleptics [8–11].

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