Remoxipride: pharmacokinetics and effect on plasma prolactin

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- 1 The pharmacokinetics of remoxipride, a new neuroleptic, were investigated in 15 healthy subjects after an intravenous infusion of 50 mg, an intramuscular injection of 100 mg and after administration of two immediate release capsules (A and B), each of 100 mg, in a cross-over study. The effect of the different remoxipride formulations on plasma prolactin concentrations was also studied.
- 2 The volume of distribution of remoxipride was $0.65 \pm 0.11 \text{ kg}^{-1}$ (mean $\pm$ s.d.). Total plasma clearance was $119 \pm 39 \text{ ml min}^{-1}$, of which $31 \pm 13 \text{ ml min}^{-1}$ was due to renal clearance. The absolute bioavailability after the i.m. and oral formulations was greater than 90%, indicating a small extent of first-pass metabolism. The mean elimination half-life was $4.8 \pm 1.4 \text{ h}$. The unbound fraction of remoxipride and the blood/plasma ratio were 0.19 ± 0.03 and 0.64 ± 0.06 , respectively.
- 3 The transient increase in plasma prolactin was similar after all four remoxipride administrations and independent of the given dose.

Keywords remoxipride prolactin man pharmacokinetics

Introduction

Remoxipride, (–)-(S)-3-bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2,6-dimethoxybenzamide hydrochloride monohydrate, is a new antipsychotic of the benzamide type (Figure 1). It is a dopamine D₂-receptor antagonist having virtually no affinity for muscarinic, adrenergic, histaminergic, serotonergic or γ -aminobutyric acid (GABA) receptors (Ögren *et al.*, 1984). Controlled clinical trials have shown that remoxipride has an antipsychotic effect, with a significantly lower frequency of extrapyramidal symptoms than haloperidol (Lapierre *et al.*, 1990; Lewander *et al.*, 1990).

Like conventional neuroleptics, remoxipride increases prolactin levels in humans, through an inhibitory effect on dopamine D₂-receptors in the anterior pituitary

(Meltzer *et al.*, 1978; Müller *et al.*, 1983). Prolactin might contribute to some of the unwanted effects of neuroleptics such as menstrual disturbances, amenorrhoea, galactorrhoea and impotence, probably associated with effects on the hypothalamic-pituitary-gonadal axis.

The aims of this study were to document the pharmacokinetics of remoxipride in conjunction with the effects of different formulations on plasma prolactin concentration.

Methods

Subjects

Fifteen healthy, non-obese Caucasian subjects (seven females and eight males) between the ages of 25 and 38 years (mean 31 years) participated in the study. All were healthy according to medical history, physical examination, ECG and laboratory tests. Lactating or pregnant women were not included.

The study was approved by the Ethics Committee of the South and West medical districts of Stockholm, and was performed according to the Declaration of Helsinki. Each volunteer gave their signed informed consent to participate.

Figure 1 Chemical structure of remoxipride [(–)-(S)-3-bromo-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-2,6-dimethoxybenzamide].

Study design

The study was designed as a three-period randomized cross-over with at least 1 week between the oral and i.m. doses. Each subject was given two capsule formulations and an intramuscular injection as single doses of 100 mg remoxipride hydrochloride monohydrate. In addition, 1 week after the last administration each subject received an intravenous infusion of 50 mg remoxipride hydrochloride monohydrate over 30 min.

Drug administration

All doses were administered at 08.00 h together with one glass of tap water. Before drug administration all subjects had fasted for a minimum of 8 h, but were allowed a glass of water at least 1 h before dosing.

To ensure adequate diuresis water intake was maintained at 150 ml h⁻¹. Lunch was served after the 3 h sample, a light meal after 6 h and dinner 9 h after drug intake. Caffeine-containing beverages were not allowed during the first 6 h of each experimental session. No other drugs or alcohol were allowed over the 48 h prior to or during each experimental session.

The two immediate-release capsules A and B were slightly different in composition and were produced and supplied by Astra Research Centre AB, Södertälje, Sweden. The intramuscular dose was injected into the gluteal muscle as a 1 ml of an aqueous solution.

The intravenous dose was administered using an infusion pump (IMED 960, volume pump) over exactly 30 min (5 ml min⁻¹). The infusion was given through an intravenous cannula in one arm and the blood samples were taken from the other arm. The solution of remoxipride for infusion was prepared aseptically immediately before administration by adding physiological saline to a stock solution. The mean actual dose given i.v. was 49.2 mg with a range of 48.0–49.5 mg. The subjects were recumbent during the infusion and the first hour thereafter.

Blood and urine sampling

Blood samples (5 ml) were drawn into Venoject® tubes for the analysis of remoxipride and prolactin. Plasma was separated by centrifugation within 1 h and transferred to polypropylene tubes (Nunc® tubes). The samples were stored at -20° C until analysed. The sampling times after oral and im drug administration were: 0, 15, 30, 45, 60 and 90 min, 2, 3, 4, 6, 8, 10, 12, 24, 26 and 30 h. After i.v. administration blood samples were taken using the 'heparin-lock' technique from an indwelling catheter over the first 6 h, after which Venoject® tubes were used. Samples were drawn just prior to dosing and at 10, 20, 30, 32, 35, 45, 60 and 90 min, 2, 3, 4, 6, 8, 10, 12, 24, 26 and 30 h after the start of the intravenous infusion.

Urine samples were collected before, 0–2, 2–4, 4–8 and 8–12 h after each dose, and at 12 h intervals up to 48 h. Total volume and pH (pHep® pH-meter) were measured after each sampling interval. All urine was refrigerated during each interval. Thereafter an aliquot was transferred to Nunc® tubes and stored at -20° C until analysed.

Adverse events

Adverse events spontaneously reported by the subject or observed by the staff were recorded, specifying the severity of each symptom. In addition, open questioning regarding adverse symptoms was performed before, 12 h after drug administration and at the end of each experimental session.

Analytical procedures

Plasma and urine concentrations of remoxipride were measured by reversed phase h.p.l.c. (Nilsson, 1990). The blood samples were analysed by the same method, except that they were homogenized in an ultrasonic bath prior to analysis. The limit of determination was defined as the drug concentration with a maximum CV of 10% and was 0.05 µmol l⁻¹ for remoxipride in all three fluids. Accuracy was estimated from the assay of spiked blank plasma samples (*n* = 12 at each concentration). The intraassay precision (C.V.) at 0.200 µmol l⁻¹ was 1%. The interassay precision was 1.8% at 0.2 µmol l⁻¹, 3.2% at 5 µmol l⁻¹ in plasma and 3.6% at 1 µmol l⁻¹ and 2.1% at 10 µmol l⁻¹ in urine. The unbound concentrations of remoxipride were measured by ultrafiltration (Amicon filters) from samples collected 1, 6 and 12 h after dosing.

Prolactin concentrations in plasma were measured using a commercial radioimmunoassay kit (Diagnostic Prod Corporation, Los Angeles, California). The limit of determination of prolactin was 5 µg l⁻¹ (0.22 nmol l⁻¹). Normal levels in females are below 25 µg l⁻¹ and in males below 20 µg l⁻¹.

Plasma concentrations of α₁-acid glycoprotein were measured by a nephelometric technique (Behring Nephelometer). The limit of determination of α₁-acid glycoprotein was 0.1 g l⁻¹ (2.4 µmol l⁻¹). Normal limits are between 0.3 and 1.0 g l⁻¹.

Pharmacokinetic calculations

Pharmacokinetic parameters based on total and unbound drug concentrations were calculated from plasma and urine data according to standard noncompartmental methods (Gibaldi & Perrier, 1982). The area under the plasma drug concentration-time curve was calculated using the logarithmic trapezoidal rule for decreasing concentrations with extrapolation to infinity by adding the calculated concentration at the last sampling time divided by the slope of the log terminal elimination phase.

Body surface area (BSA) was calculated from

$$\text{BSA (m}^2\text{)} = \frac{\text{Weight}^{0.425}}{\text{(kg)}} \times \frac{\text{Height}^{0.725}}{\text{(cm)}} \times 71.84/10000$$

(DuBois & DuBois, 1916).

Plasma drug clearance was normalized to 1.73 m² BSA.

For prolactin, the maximum plasma concentration (*C*_{max} (PRL)), the time to *C*_{max} (PRL) (*t*_{max} (PRL)), AUC (0,12 h) PRL, AUC (0,24 h) PRL and the time above the normal upper limit over 24 h were calculated for each subject. The initial decline in prolactin concentration was described by an apparent half-life (*t*_{1/2}PRL) after subtraction of individual baseline values.

Statistical methods

Hypotheses concerning the pharmacokinetic parameters were analysed using Wilcoxon sign rank statistics (Lehmann, 1975).

Calculations of the absolute bioavailability of remoxipride were performed on the log transformed data. Confidence intervals (95%) based on the *t*-distribution were calculated. Prolactin concentrations are presented as Wilcoxon median values (Hollander & Wolfe, 1973; Lehmann, 1975).

Results

Plasma concentrations of remoxipride declined mono-exponentially after each mode of administration (Figure 2). The mean ($\pm$ s.d.) clearance was 119 ± 39 ml min⁻¹. After correction for body surface area, it was 112 ± 34 ml min⁻¹ 1.73 m⁻². Approximately 25% of the i.v. dose was excreted unchanged by the kidneys. Interindividual variability following i.v. infusion was 3.7 fold in CL (range 54–198 ml min⁻¹) and 2 fold in *V*_{ss} (mean 0.65 ± 0.11 l kg⁻¹, range 0.47–0.91 l kg⁻¹). Values of *V*_{ss} were similar in men and women. However, the females had slightly lower normalized clearance values than the males (92 ± 27 vs 130 ± 31 ml min⁻¹ 1.73 m⁻²). The value of *t*_{1/2} varied between 2.6 and 8.2 h and urinary excretion of unchanged drug varied between 14 and 40% following i.v. infusion. Urinary recoveries and renal clearances of remoxipride were similar after all four administrations (Table 1). Urinary pH varied between 4.8 and 7.5 with a mean of 6.1.

The mean fraction of remoxipride unbound in plasma (*f*_u) was 0.19 ± 0.03 . The value was slightly higher at 1 h compared with 12 h after the dose. Following i.v. administration, *f*_u was 0.21 at 1 h and 0.17 at 12 h. Mean concentrations of α_1 -acid glycoprotein in plasma ranged from 0.7–0.8. The unbound fraction of remoxipride did

Figure 2 Mean ($\pm$ s.d.) plasma concentration of remoxipride following single doses of remoxipride: i.m. 100 mg (...○...), capsule A 100 mg (—△—), capsule B 100 mg (---▽---) and i.v. infusion 50 mg (—□—) (*n* = 15).

not differ significantly after the four administrations. The mean ($\pm$ s.d.) blood/plasma ratio was 0.64 ± 0.06 .

The mean absolute bioavailability of remoxipride was greater than 90% for both oral capsules and it was 100% for the i.m. dose (Table 1). The oral capsules and the i.m. formulation were bioequivalent with respect to both rate and extent.

Prolactin

Plasma prolactin concentrations increased following the administration of remoxipride and similar changes were observed after all four remoxipride administrations, although the i.v. dose was half the available oral dose. As female subjects have higher prolactin concentrations than males data for the two groups are presented separately (Figures 3a, b). The increase of prolactin was transient and the levels returned to baseline in female and male subjects within about 10 h and 4 h, respectively (Table 2).

Table 1 Mean (s.d.) pharmacokinetic parameters describing the time-curves of plasma remoxipride following single doses of remoxipride : i.v. infusion 50 mg, i.m., Capsule A and Capsule B 100 mg (15 healthy subjects)

	<i>i.v.</i> (50 mg)	<i>i.m.</i> (100 mg)	<i>Capsule A</i> (100 mg)	<i>Capsule B</i> (100 mg)
<i>F</i> * (%)		99.7 (91,109)	92.6 (83,103)	90.6 (76,108)
AUC (μmol l ⁻¹ h)	17.3 $\pm$ 6.9	34.8 $\pm$ 11.7	32.6 $\pm$ 12.2	32.2 $\pm$ 13.4
<i>t</i> _{1/2} (h)	4.8 $\pm$ 1.4	4.5 $\pm$ 1.0	4.8 $\pm$ 1.4	4.6 $\pm$ 1.3
<i>C</i> _{max} (μmol l ⁻¹)	2.9 $\pm$ 0.7	5.1 $\pm$ 1.1	4.7 $\pm$ 1.1	4.6 $\pm$ 1.1
<i>t</i> _{max} (h)	(0.6 $\pm$ 0.1)	1.0 $\pm$ 0.7	1.2 $\pm$ 0.5	1.2 $\pm$ 0.5
CL _R (ml min ⁻¹)	30.9 $\pm$ 13.1	26.5 $\pm$ 9.8	27.0 $\pm$ 9.5	28.3 $\pm$ 13.1

* Geometric mean and 95% CI.

Table 2 Mean (s.d.) kinetic parameters describing the time-course of plasma prolactin following a single dose of remoxipride in seven female and eight male healthy subjects (statistically significant differences are indicated)

	<i>i.v.</i> (50 mg)	<i>i.m.</i> (100 mg)	Capsule A (100 mg)	Capsule B (100 mg)
<i>Females</i>				
$C_{\max}$ ($\mu\text{g l}^{-1}$)	230 $\pm$ 138	154 $\pm$ 19	202 $\pm$ 76	212 $\pm$ 41
$t_{1/2}$ (h)	0.7 $\pm$ 0.2	0.6 $\pm$ 0.2	0.9 $\pm$ 0.3	0.9 $\pm$ 0.1
	P = 0.036			
AUC (0,12 h) ($\mu\text{g l}^{-1} \text{ h}$)	871 $\pm$ 295	690 $\pm$ 163	844 $\pm$ 320	829 $\pm$ 419
AUC (0,24 h) ($\mu\text{g l}^{-1} \text{ h}$)	1090 $\pm$ 351	889 $\pm$ 258	1046 $\pm$ 384	1027 $\pm$ 415
Time above normal limits ($> 25 \mu\text{g l}^{-1}$) (h)	11.6 $\pm$ 5.8	11.8 $\pm$ 6.5	12.1 $\pm$ 6.1	12.0 $\pm$ 5.8
<i>Males</i>				
$C_{\max}$ ($\mu\text{g l}^{-1}$)	78 $\pm$ 32	82 $\pm$ 20	64 $\pm$ 32	71 $\pm$ 24
$t_{\max}$ (h)	0.6 $\pm$ 0.1	0.6 $\pm$ 0.1	0.9 $\pm$ 0.1	0.9 $\pm$ 0.1
	P = 0.010			
	P = 0.014			
	P = 0.22			
	P = 0.022			
AUC (0,12 h) ($\mu\text{g l}^{-1} \text{ h}$)	305 $\pm$ 113	278 $\pm$ 70	250 $\pm$ 98	281 $\pm$ 90
AUC (0,24 h) ($\mu\text{g l}^{-1} \text{ h}$)	420 $\pm$ 165	386 $\pm$ 115	357 $\pm$ 121	382 $\pm$ 126
Time above normal limits ($> 20 \mu\text{g l}^{-1}$) (h)	6.8 $\pm$ 5.3	5.1 $\pm$ 2.6	4.5 $\pm$ 2.6	5.5 $\pm$ 2.4

Prolactin $t_{\max}$ was significantly shorter than remoxipride $t_{\max}$ following administration of the *i.m.* dose and after capsules A and B. The half-life of prolactin was similar after all four treatments with a mean $\pm$ s.d. value of 1.9 ± 0.6 h. This was considerably shorter than the remoxipride half-life of 4.5–4.8 h.

Adverse events

Tiredness, restlessness, headache and concentration difficulties were the most frequently reported symptoms (Table 3). Less frequent and severe adverse events were reported following the *i.v.* administration.

Discussion

The results demonstrate that remoxipride has a high oral bioavailability with negligible first-pass metabolism. Remoxipride is a single enantiomer and no active metabo-

Table 3 Number of subjects (out of 15) reporting mild, moderate and severe subjective adverse events based on open questioning. The numbers of severe events are shown in parentheses

	<i>i.v.</i> (50 mg)	<i>i.m.</i> (100 mg)	Capsule A (100 mg)	Capsule B (100 mg)
Tiredness	2	7 (3)	8 (4)	4 (1)
Restlessness	1	4	3	3 (1)
Headache	2	2 (1)	3	2
Concentration difficulties	–	3	–	2

lites have been reported (Widman *et al.*, 1990). It is a low clearance drug with a plasma clearance of $112 \text{ ml min}^{-1} 1.73 \text{ m}^{-2}$ and a non-renal elimination of 75%. Pharmacokinetic parameters based on total drug concentration were similar to those reported after *i.v.* administration of 20 mg (Grind *et al.*, 1989).

An unbound renal clearance of 160 ml min^{-1} , which

Figure 3 Wilcoxon median plasma prolactin concentrations following single doses of remoxipride: i.m. 100 mg (...○...), capsule A 100 mg (—△—), capsule B 100 mg (---▽---) and i.v. infusion 50 mg (—□—) a) Males ($n = 8$), b) Females ($n = 7$).

is higher than the glomerular filtration rate, indicates that remoxipride undergoes tubular secretion. Widerlöv *et al.* (1989) showed that urinary excretion of remoxipride can be increased by acidifying the urine. These findings suggest that remoxipride is both secreted and reabsorbed but that secretion exceeds reabsorption. In this study urinary pH was relatively stable and urine volumes and pH were similar during the four study sessions.

The blood/plasma concentration ratio of remoxipride was 0.6, suggesting very little association with the formed elements of blood. Like many other basic drugs, remoxipride is bound in plasma mainly to α_1 -acid glycoprotein (Widman, personal communication).

One subject was shown to be a slow hydroxylator of debrisoquine. She also presented with the highest AUC and longest $t_{1/2}$ of remoxipride in association with more adverse events such as restlessness, slurred speech, blurred vision and headache. Her data contributed signifi-

cantly to the overall 3.7-fold variability in AUC. Excluding her value the variability decreased to 2.5-fold.

Tiredness was the most reported adverse event followed by restlessness. Fewer side-effects were reported after i.v. administration when lower plasma drug concentrations were obtained.

Plasma prolactin concentrations show a degree of diurnal variation. However, these fluctuations, as measured after a placebo dose, are negligible in comparison to the increase seen after administration of neuroleptics (von Bahr *et al.*, 1991). In the present study maximum prolactin release was observed following the i.v. dose of 50 mg remoxipride. Dose-related increases in $C_{\max, \text{PRL}}$ values occurred after doses of remoxipride from 0.1 to 100 mg (Grind *et al.*, 1989). Maximal plasma prolactin concentrations in male subjects of 60–70 $\mu\text{g l}^{-1}$ have been noted after single oral doses of 50–140 mg remoxipride (von Bahr *et al.*, 1991; Widerlöv *et al.*, 1989; calculations based on results by Farde *et al.*, 1988). Females were also studied by von Bahr *et al.* (1991) with similar results as in our study.

Therapeutic oral doses of remoxipride for the treatment of schizophrenia start at 150 mg twice daily (conventional capsule). Our results indicate that maximal prolactin release is obtained following the first dose. During continuous administration of remoxipride 200 mg twice daily in schizophrenic patients $C_{\max, \text{PRL}}$ was not significantly different from that after a single 200 mg dose (Tench *et al.*, 1990).

The kinetics of prolactin after administration of neuroleptic drugs is not fully understood. In this study we observed a shorter $t_{\max, \text{PRL}}$ compared with the $t_{\max}$ of remoxipride. This might suggest that once a critical concentration of remoxipride is reached, a maximal release of prolactin is obtained. This suggestion is also supported by the shorter half-life of prolactin compared with the half-life of remoxipride. However, confounding these observations is the comparison of the half-life of 1.9 h in the present study with a value of 5–20 min reported after exogenous prolactin administration (Crosignani & Ferrari, 1987; Franz, 1978). Several factors thus seem to be involved in the prolactin response to neuroleptics.

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