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The pharmacokinetics of remoxipride and metabolites in patients with various degrees of renal function

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1 The pharmacokinetics of remoxipride, a new neuroleptic, were investigated in an open study with three parallel groups. Twenty-one patients with severely impaired (Cl_{Cr} < 25 ml min^{-1}), moderately impaired (CL_{Cr} 25–50 ml min^{-1}) and normal (Cl_{Cr} > 65 ml min^{-1}) renal function were evaluated. A single oral dose of remoxipride hydrochloride 100 mg was administered, and blood and urine were collected over 48 h. Concentrations of remoxipride and metabolites were measured by h.p.l.c.

2 In patients with severely decreased renal function, the AUC and C_{max} of remoxipride were increased significantly, and $t_{1/2}$ was prolonged, as compared with the control patients. The renal clearance and urinary recovery of the unchanged drug were significantly diminished.

3 The unbound fraction of remoxipride in plasma was decreased in patients with renal failure, in association with a disease-related increase in α_1-acid glycoprotein. In spite of a 25% recovery of unchanged drug in the urine in patients with normal renal function, the AUC of unbound drug was twice as high in patients with severely impaired renal function.

4 A strong correlation between creatinine clearance and renal drug clearance was observed indicating a direct relationship between kidney function and the renal clearance of remoxipride.

5 Remoxipride was the predominant compound in plasma as well as in urine in patients with severely decreased as well as normal renal function. In patients with severely decreased renal function, remoxipride and all five pharmacologically inactive metabolites showed increased peak plasma concentrations, delayed t_{max}, increased AUC, prolonged half-lives and decreased renal clearance.

Keywords remoxipride metabolites man pharmacokinetics renal function neuroleptic α_1-acid glycoprotein protein binding

Introduction

Remoxipride, [(S)-3-bromo-*N*-[(ethyl-2-pyrrolidinyl)-methyl]-2,6-dimethoxy benzamide, is a new antipsychotic of the benzamide type (Figure 1). 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).

Remoxipride is a low clearance drug which is eliminated both by metabolism and by renal excretion. Renal elimination accounts for about 25% of the dose in subjects with normal renal function (Movin-Osswald *et al.*, 1991). The drug is bound in plasma mainly to α_1-acid glycoprotein, the concentration of which can be affected by renal disease. The metabolic pathways of remoxipride in man are shown in Figure 1 (Widman *et al.*, 1993) and include oxidation, hydroxylation and deethylation. The major identified metabolic pathway of remoxipride involves oxidation of the carbon alpha to the pyrrolidine nitrogen. Remoxipride given as an S-isomer was also identified in the urine as the S-isomer without any trace of the R-isomer, indicating that no metabolic inversion occurs (Nilsson, personal com-

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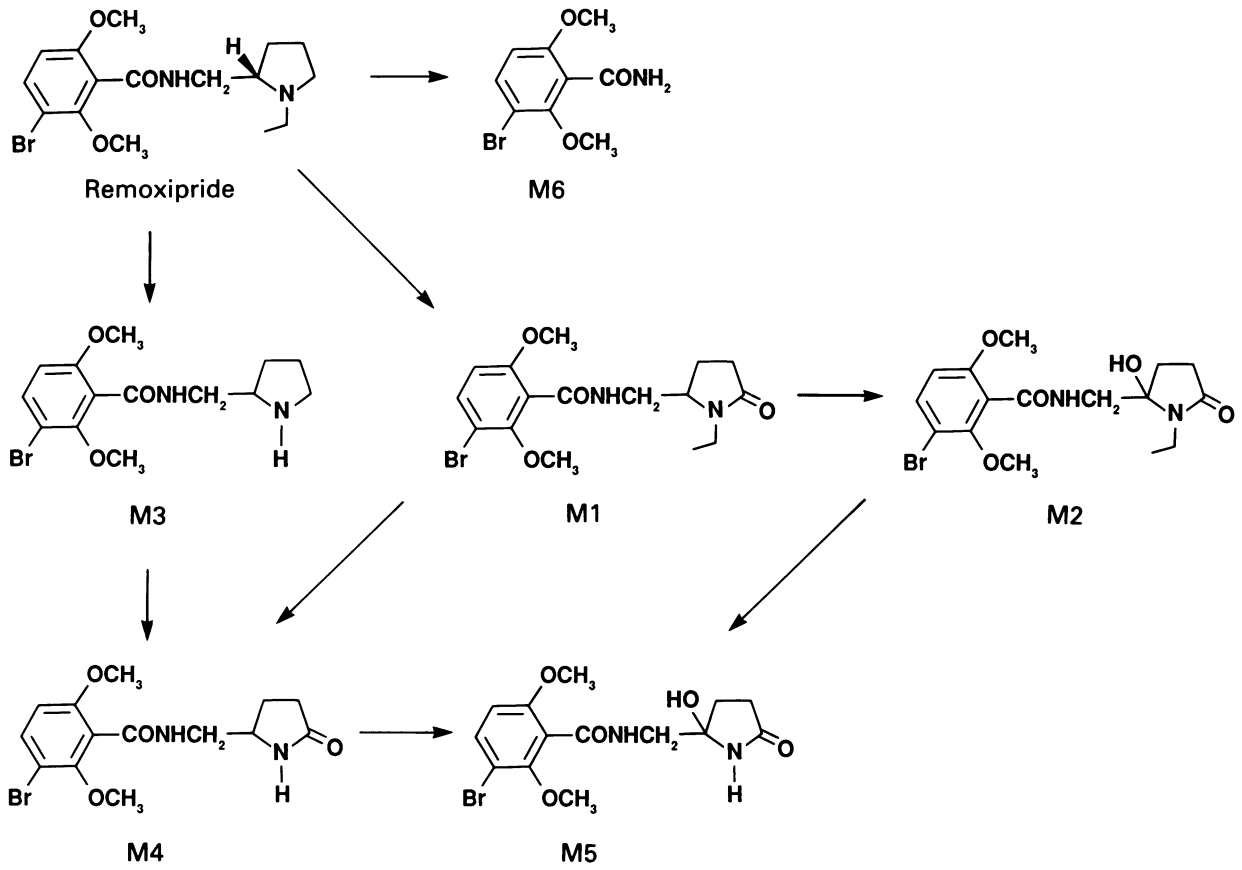

Figure 1 Proposed metabolic pathways of remoxipride in man.

munication). Remoxipride was shown to be the predominant compound in plasma and urine after administration to healthy young volunteers. About 60% of the urinary recovery has been identified (Widman *et al.*, 1993). None of these metabolites has been found to be active on the dopamine D_2-receptor (Widman *et al.*, 1993).

The aim of this study was to investigate the effects of renal dysfunction on the pharmacokinetics of remoxipride and its metabolites following a single oral dose.

Methods

Patients

Twenty-one male and female non-obese, non-psychiatric patients, aged 35 to 66 years, were included in the evaluation. They had renal and/or other diseases which were stable and most were receiving multiple medication.

Seven patients had severely impaired renal function (RI) with a creatinine clearance/1.73 m^2 (CL_{Cr}) between 5 and 25 ml min^{-1} and seven patients had moderately impaired renal function (RII) with a CL_{Cr} between 25–50 ml min^{-1}. A control group (C) included seven subjects with normal renal function and a CL_{Cr} above 50 ml min^{-1}. For the evaluation of drug metabolites six of the seven patients with severely impaired renal function and the seven control patients with normal renal function were studied. In the control group the seven subjects with normal renal function included five healthy volunteers and two patients with stable hypertension. Demographic information about the patients is presented in Table 1. Assessment of renal impairment was based on a medical history and on the average of two measurements of creatinine clearance varying less than 20% performed within the last month preceding dosing. Serum β_2-microglobulin was measured in the predose sample taken on the morning of the study day.

All patients had normal liver function test results (SGPT < 90 iu ml^{-1}) and normal ECG. Patients on dialysis, with CL_{Cr} < 5 ml min^{-1}, acute infection, major chronic inflammatory disease, nephrotic syndrome, diabetes, or receiving concomitant treatment with neuroleptics, cimetidine or antiarrhythmic drugs were excluded.

Most patients received one or more drugs commonly used in this patient population. The drugs used that are known to interact with cytochrome P-450 debrisoquine hydroxylase (CYP P450 2D6), which also metabolizes remoxipride (Steiner *et al.*, 1989), were trimipramine (n = 1) and propranolol (n = 1). Furthermore, trimipramine, propranolol and prazosin (n = 2) bind to α_1-acid glycoprotein to which remoxipride is also bound (Sigurdsson & Nilsson, 1985).

Values of CL_{Cr}, serum β_2-microglobulin and serum creatinine were significantly different between the three patient groups RI, RII and C. The patients with impaired renal function (RI and RII) were slightly older than the C patients whereas body surface area (BSA) was similar.

Table 1 Patient characteristics (mean ± s.d.)

Renal impairment group	*Age (years)*	*BSA (m^2)*	*CL_{Cr} (ml min^{-1})*	*C_{Cr} (mg l^{-1})*	*Serum β_2-microglobulin (mg l^{-1})*
RI: Severe (n = 7)	53 ± 13	1.8 ± 0.2	11.3 ± 4.7	59 ± 24	13.9 ± 4.1
RII: Moderate (n = 7)	55 ± 6	1.8 ± 0.2	41.9 ± 8.8	15 ± 2	3.2 ± 1.3
C: Control (n = 7)	39 ± 13	1.8 ± 0.2	88.9 ± 16.4	9 ± 1	1.5 ± 0.4
	NS[a,c] $P < 0.05$[b]	NS[a–c]	$P < 0.005$[a–c]	$P < 0.005$[a,b] $P < 0.05$[c]	$P < 0.005$[a–c]

Comparisons: [a]RI–C. [b]RII–C. [c]RII–RI.

The study was approved by the Ethics Committee of the Algemeen Ziekenhuis St Jan, Brugge, Belgium and was performed according to the Declaration of Helsinki. Each patient gave his or her informed consent to participate.

Study design

The study was performed as an open single dose study, with a parallel group design. Immediate-release capsules of remoxipride hydrochloride monohydrate 100 mg were supplied by Astra Arcus AB. One capsule was administered at 08.00 h together with one glass of tap water (150 ml). Before drug administration the patients had fasted for a minimum of 8 h, but they had taken a glass of water at least 1 h before dosing. To ensure adequate diuresis, water intake was maintained at 150 ml h^{-1}. Lunch and dinner were served at 3 and about 9 h after drug intake.

Patients receiving other drug therapy discontinued this treatment at least 12 h prior to and up to a minimum of 3 h after remoxipride dosing. Intake of alcohol was not allowed from 48 h prior to and during the study.

Blood and urine sampling

Blood samples (5–10 ml) were drawn into Venoject® tubes for the analysis of remoxipride. Plasma was separated by centrifugation within 1 h and transferred to polypropylene tubes (Nunc® tubes). The samples were stored at −20° C until assayed. The sampling times were: 0, 15, 30, 45, 60 and 90 min, 2, 3, 4, 6, 8, 10, 12, 24, 32, and 48 h. Plasma concentrations of α_1-acid glycoprotein were measured in the pre-dose sample.

Urine samples were collected before and from 0–2, 2–4, 4–6, 6–8, 8–10, 10–12 h after dosing, and at 12 h intervals up to 48 h. Total volume and pH 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 patient or observed by the staff were recorded, specifying the severity of each symptom. In addition, open questioning regarding adverse symptoms was performed before, about 12 h after drug administration and at the end of the experimental session.

Analytical procedures

Measurement of remoxipride Plasma and urine concentrations of remoxipride were measured by reversed phase h.p.l.c. after liquid–liquid extraction (Nilsson, 1990). At 0.2 μmol l^{-1} the within-run precision was 1.0% and the accuracy was 101.5% (n = 12). The corresponding results at 2 μmol l^{-1} were 0.9% and 100.0%, respectively. The between-run precision, calculated for control samples assayed each day samples from the present study were determined, was 2.7% (plasma, 5 μM), 2.1% (urine, 1 μM) and 1.7% (urine, 10 μM). The limit of quantification was 0.05 μM. Unbound plasma concentrations of remoxipride were determined using the same method after ultrafiltration (Amicon MPS-1) step.

Measurement of metabolites A similar method was used for the assay of the metabolites M1, M2, M4 and M5. Internal standard was added to the sample and thereafter the biological fluid was alkalized using carbonate buffer pH 11 and the compounds were extracted into chloroform. After centrifugation, the organic phase was transferred to another tube and evaporated to dryness. The residue was dissolved in pH 2 phosphate buffer and injected into the chromatographic system. The chromatographic column (100 × 4.6 mm i.d.) was packed with 3 μ octadecylsilica (Nucleosil C18 120-3, Macherey-Nagel, Düren, Germany) and the mobile phase was acetonitrile-phosphate buffer pH 2 (21:79, v/v) with the addition of 0.2 mM dimethyloctylamine (DMOA) and 0.5 mM sodium nonyl sulphate (NS). The compounds were detected by their u.v.-absorbance at 206 nm. The absolute recoveries were quantitative (> 95%) for all compounds except M5 (70%) and the within-run precision was 3–5% (0.8–1.5 μmol l^{-1}). The limit of quantification was 0.05 μmol l^{-1} for all compounds.

A separate method involving a slight modification of that described above was developed for the determination of M3. The organic phase for this extraction was a mixture of heptafluorobutanol (3% v/v) and isopropanol (1% v/v) in isooctane and the chromatographic mobile phase was acetonitrile-phosphate buffer pH 2 (22:78, v/v) with 0.55 mM DMOA and 0.5 mM NS. The absolute

recovery was 94%, the within-run precision was 1% (1 μM) and the limit of quantification was 0.02 μM. M6 was not measured since it only appeared in very small amounts (Widman *et al.*, 1993).

Measurement of α_1-acid glycoprotein Plasma concentrations of α_1-acid glycoprotein were measured by nephelometry (Behring Nephelometer). The limit of determination was 0.1 g l^{-1} (2.4 μmol l^{-1}). Normal values are between 0.3 and 1.0 g l^{-1}.

Pharmacokinetic calculations

Pharmacokinetic parameters based on total and unbound remoxipride and metabolite 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; m^2) was calculated as BSA = $\text{Weight}^{0.425} \times \text{Height}^{0.725} \times 71.84/10000$, with weight in kg and height in cm (duBois & duBois, 1916). Plasma drug clearance was normalized to 1.73 m^2 BSA.

The fraction unbound (*fu*) of remoxipride in plasma was calculated from unbound concentration (*Cu*) divided by total concentration in plasma (*Cp*) from samples collected 1, 6 and 12 h after dosing. A mean *fu* was calculated for each individual from the three determinations.

Statistical methods

The one-sided Wilcoxon rank sum test (Lehmann, 1975) was used to evaluate differences in the pharmacokinetic parameters between the groups (e.g. patients with moderately and severely decreased renal function and control patients). In the evaluation of patient characteristics, and for the difference in the pharmacokinetic parameters of the metabolites two-sided Wilcoxon rank sum tests were used. An outcome with a *P* value less than 0.05 was considered significant.

The measure of association between CL_R and CL_{Cr} was Spearman's rank correlation coefficient (Lehmann, 1975). To obtain an estimate of the linearity of the slope, the resistant regression method described by Emerson & Hoaglin (1983) was used. The half-slope ratio is the ratio between the estimates of the slopes in the upper and lower half of the data with respect to the independent variable using the method mentioned above. It gives a measure of how straight the relationship between two variables is. If the half-slope ratio is close to 1, the relationship can be taken as straight, while a value far from 1 indicates a departure from the linearity.

Results

Pharmacokinetics of remoxipride

Remoxipride AUC and C_{max} values were significantly increased and $t_{1/2}$ was prolonged in patients with severely decreased renal function (RI) compared with both control patients (C) and patients with moderately decreased renal function (RII) (Figure 2, Table 2). The mean AUC was three times higher for RI compared with C patients, while their renal function was 12% of that in the C group. The residual areas were below 5% in all groups. The interindividual variability in AUC and $t_{1/2}$ was larger in the renal patients (3- and 4-fold) compared with the control patients (2-fold).

Table 2 Pharmacokinetic parameters of remoxipride in patients with varying degrees of renal impairment (mean ± s.d.)

Pharmacokinetic parameter/ Renal function	*Patient group* *RI Severe* (n = 7)	*RII Moderate* (n = 7)	*C Normal* (n = 7)	*Statistics* (P value)*
CL_{Cr} (ml min^{-1})	11 ± 5	41 ± 8	89 ± 16	$< 0.001^{a-c}$
C_{max} (μmol l^{-1})	9.3 ± 2.3	7.7 ± 2.7	5.5 ± 1.1	$< 0.005^{a}$ $< 0.05^{b}$, NS^{c}
t_{max} (h)	1.4 ± 0.9	0.9 ± 0.4	0.8 ± 0.2	NS^{a-c}
AUC (μmol l^{-1} h)	123 ± 60	63 ± 34	39 ± 9	$< 0.005^{a}$, NS^{b} $< 0.05^{c}$
$t_{1/2}$ (h)	9.9 ± 3.8	6.1 ± 2.6	5.1 ± 1.6	$< 0.005^{a}$, NS^{b} $< 0.005^{c}$
Ae(48 h) (%)	8.4 ± 3.5	14 ± 8	24 ± 8	$< 0.001^{a}$ $< 0.05^{b}$, NS^{c}
CL_R (ml min^{-1})	3.7 ± 2.9	9.3 ± 3.8	23.6 ± 7.0	$< 0.005^{a.b}$ $< 0.01^{c}$
α_1-acid glycoprotein (g l^{-1})	1.7 ± 0.7	1.3 ± 0.3	0.8 ± 0.3	$< 0.01^{a}$ $< 0.05^{b}$, NS^{c}
Fraction unbound	0.14 ± 0.04	0.17 ± 0.01	0.21 ± 0.06	$< 0.05^{a}$, $NS^{b.c}$
Unbound AUC (μmol l^{-1} h)	15.8 ± 7.8	10.3 ± 4.8	8.6 ± 3.1	$< 0.05^{a}$, $NS^{b.c}$

*Comparisons: [a]RI–C. [b]RII–C. [c]RI–RII.

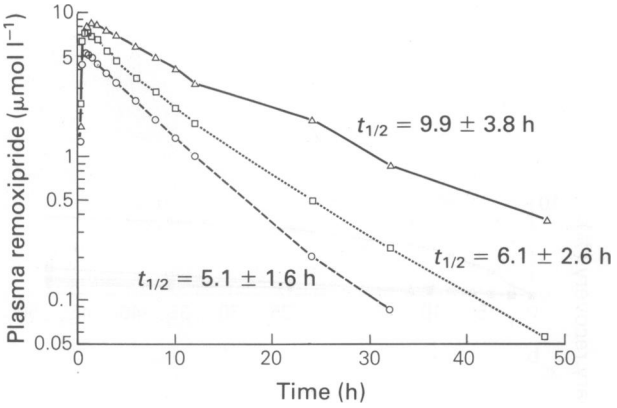

Figure 2 Mean plasma remoxipride concentrations (μmol l^{-1}) after oral administration of remoxipride 100 mg to patients with severely impaired (RI, △), moderately impaired (RII, □) and normal renal function (C, ○).

Plasma concentrations of α_1-acid glycoprotein were significantly elevated in the patients with renal impairment and the binding of remoxipride was increased, resulting in a decreased unbound fraction (Table 2). This change in protein binding was taken into account by calculating the unbound AUC (AUCu), which in the RI patients was almost twice that in the control patients.

Calculated volume and clearance values are presented in Table 3. *V/F* was decreased but *Vu/F* was unchanged. Based on a bioavailability (*F*) of 0.90 (Movin-Osswald & Hammarlund-Udenaes, 1991), unbound metabolic clearance was also calculated. The unbound metabolic clearance was decreased to 50% in the RI patients, assuming no change in bioavailability.

The renal clearance of remoxipride decreased in direct proportion to the decrease in renal function, as measured by CL_{Cr}. The association between CL_{Cr} and renal clearance/1.73 m^2 (CL_R) is shown in Figure 3 (r = 0.89, $P < 0.01$, slope = 0.29, half-slope-ratio = 1.24).

The urinary recovery of unchanged remoxipride was also decreased in patients with decreased renal function (Figure 4, Table 2). Urine pH varied between 4.2 and 8.6 with mean values of 6.7, 6.4 and 6.2 in RI, RII and C groups, respectively. Mean urine volumes were 1.9, 1.7 and 1.6 l during 24 h in RI, RII and C patients, respectively.

Pharmacokinetics of remoxipride and metabolites

The pharmacokinetics of remoxipride and metabolites were compared in two groups namely the patients with normal (C) and severely impaired renal function (RI). Remoxipride was the predominant compound in plasma and urine in both groups (Figures 5 and 6). The

Table 3 Calculated distribution volumes and clearance values of remoxipride in patients with varying degrees of renal impairment (mean ± s.d.)

	RI (n = 7)	*RII* (n = 7)	*C* (n = 7)	*Statistics** (P *value*)
V/F (l)	30.2 (±9.4)	37.4 (±16.2)	44.3 (±8.3)	$< 0.05^a$, $NS^{b,c}$
Vu/F (l)	219.8 (±54.3)	219.7 (±82.7)	215.3 (±54.4)	NS^{a-c}
CL/F (ml min^{-1})	41.7 (±25.2)	77.7 (±37.2)	104.6 (±25.0)	$<0.005^a$, $<0.05^c$, NS^b
CLu/F (ml min^{-1})	283.5(±103.2)	458.3 (±208.0)	537.6(±268.8)	$<0.01^a$, $NS^{b,c}$
CLu (ml min^{-1})†	315.0(±114.6)	509.3 (±231.1)	597.3(±298.6)	$< 0.01^a$, $NS^{b,c}$
CLu_R (ml min^{-1})	24.0 (±13.5)	55.0 (±20.3)[d]	113.4 (±33.6)	$< 0.0005^a$, $<0.001^b$, $<0.01^c$
CLu_M (ml min^{-1})[d]	290.9(±104.7)	493.3(±224.8)[d]	483.9(±277.2)	NS^{a-c}

†*F* was assumed to be 0.90 in all groups.
*Comparisons: [a]RI–C. [b]RII–C. [c]RI–RII.
[d] $n = 6$.

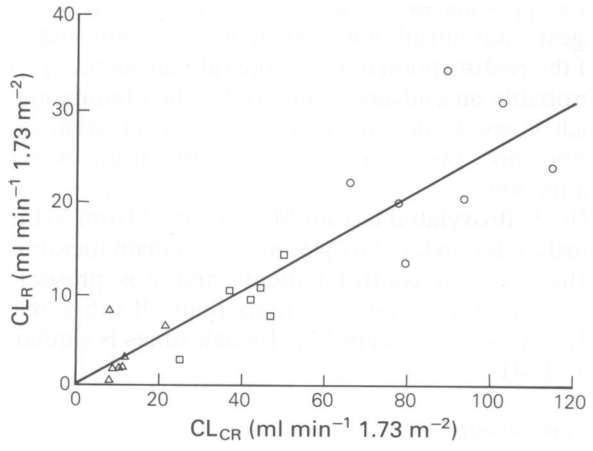

Figure 3 Renal clearance (CL_R) of remoxipride *vs* creatinine clearance (CL_{Cr}) in patients with severely impaired (RI, △), moderately impaired (RII, □) and normal renal function (C, ○).

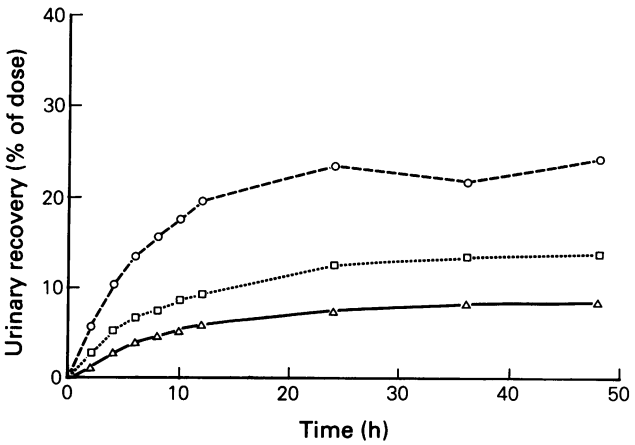

Figure 4 Mean cumulative urinary recovery of remoxipride in patients with severely impaired (RI, △), moderately impaired (RII, □) and normal renal function (C, ○).

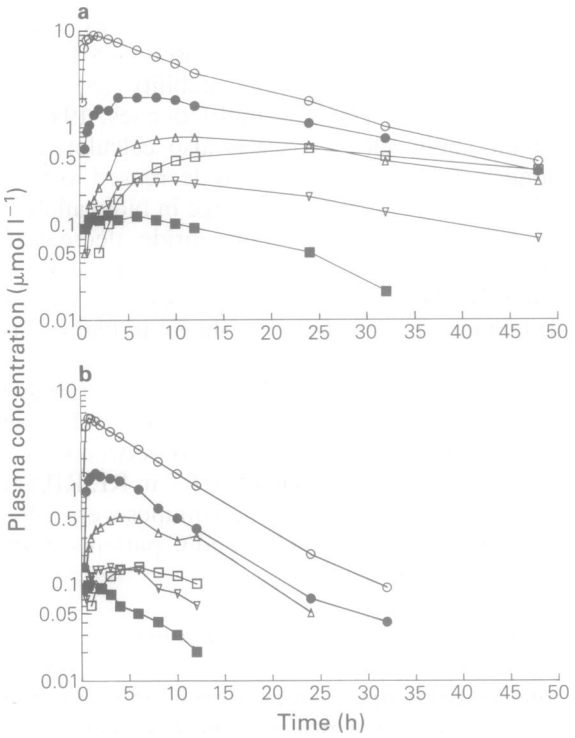

Figure 5 Mean concentrations of remoxipride and metabolites in plasma following a single oral 100 mg dose of remoxipride to patients with a) severely impaired and b) normal renal function. ○ remoxipride, ● M1, ■ M3, ▽ M4, △ M2, □ M5.

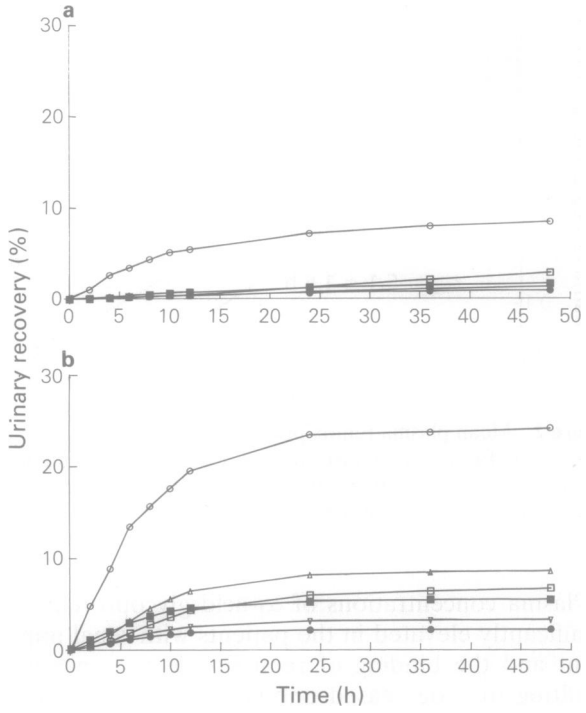

Figure 6 Mean cumulative urinary recovery of remoxipride and metabolites (0–48 h) following a single oral 100 mg dose of remoxipride to patients with a) severely impaired and b) normal renal function. ○ remoxipride, ● M1, ■ M3, ▽ M4, △ M2, □ M5.

order of predominance of the metabolites in plasma was also similar in the two groups. Both remoxipride and metabolites showed similar increases in peak plasma concentration, delayed t_{max}, increases in AUC ($P < 0.05$), prolonged half-times ($P < 0.05$) and decreases in renal clearance ($P < 0.005$). Detectable plasma concentrations of remoxipride and all metabolites except M3 were observed after 48 h in the renal patients, whereas in the control patients none of the compounds were detectable in the 48 h samples. The cumulative urinary recovery of remoxipride and metabolites over 48 h was 16% in uraemic patients as compared with 51% in control patients (Figure 6).

The interindividual variability in the pharmacokinetic parameters of remoxipride and metabolites was larger within the RI group as compared with within the C group. The total AUCs were 3 to 7 times higher in RI patients for remoxipride, M1, M2, M3, M4 and M5. The estimated accumulation ratios from a single dose to steady state of remoxipride and its metabolites were between 1.8 to 3.3 in RI patients and between 1.2 to 2.0 in C patients.

The oxidized metabolite M1 formed from remoxipride had the highest concentration in plasma in both patient groups (Figure 5). The half-life of M1 was similar to the half-life of remoxipride, 6 h in the control group and 13 h in the renal group, indicating formation rate limitated kinetics. The renal clearance of the lactam M1 decreased in proportion to the decrease in CL_{Cr} and was very low in both patient groups, indicating extensive reabsorption. This metabolite was excreted to the lowest extent in the urine of all the identified metabolites, which is consistent with it being metabolized further.

The half-time of M3, the *N*-deethylated metabolite in plasma, was similar to that of remoxipride, again indicating formation rate limited metabolite kinetics. M3 was found in low concentrations in plasma. It had a high renal clearance in both patient groups compared with their creatinine clearance, indicating extensive secretion.

M1 and M3 may be further metabolized to the *N*-deethylated lactam M4, which was found in small amounts in the urine. Its renal clearance indicates that reabsorption occurs. The half-time of M4 was longer compared with remoxipride in both renal and control patients. This metabolite seems to be the only metabolite showing elimination rate-limited kinetics.

M4 is hydroxylated to the *N*-deethylated hydroxy-substituted lactam M5. The renal clearances of M5 in RI and C patients of 5.3 and 85 ml min^{-1} respectively, suggests that filtration was the main excretion route, or that the reabsorption matches the tubular secretion. M5 is probably an endstage metabolite, the elimination of which is solely dependent on its renal clearance. Its kinetics are, therefore, markedly influenced by renal dysfunction.

The hydroxylated lactam M2 is formed from M1 and is further deethylated to M5. M2 was a main metabolite in the urine in control patients and was present in plasma in higher concentrations than all other metabolites in plasma except M1. Its half-times is similar to that of M1.

Adverse events

Remoxipride was well tolerated in all patients. No adverse events were observed, spontaneously reported or reported on open questioning.

Discussion

Although only 25% of a dose of remoxipride is excreted in urine as unchanged drug, significant differences in pharmacokinetic parameters were seen in patients with severely decreased renal function as compared with control patients. The 3-fold increase in AUC in the RI group was higher than expected based on the decrease in renal function. The increase could be due to changes in the metabolism and/or changes in protein binding.

Renal failure has been shown to alter the concentrations of plasma proteins including α_1-acid glycoprotein, and thereby to alter the plasma protein binding of many drugs (Piafsky *et al.*, 1978; Tozer, 1984). Accordingly, the unbound fraction of remoxipride was decreased in the patients with renal failure in association with an increased plasma concentration of α_1-acid glycoprotein. As remoxipride is a low clearance drug, (Movin-Osswald & Hammarlund-Udenaes, 1991), a decreased unbound fraction results in a decreased systemic clearance. Furthermore, an increase in plasma protein binding leads to a decreased volume of distribution (V).

The mean renal unbound clearance of remoxipride in the control patients was 113 ml min^{-1} and the CL_{Cr} was 89 ml min^{-1}, which indicates that tubular secretion of remoxipride exceeds its reabsorption (Widerlöv *et al*, 1990). The mean renal unbound clearance CLu_R, in RI patients was 24 ml min^{-1}. Based on CL_{Cr} values in the two patient groups, the CLu_R would have decreased to 14 ml min^{-1}. These findings indicate that the patients with severely impaired renal function have a larger decrease in filtration than in tubular secretion or that they have a smaller degree of reabsorption of remoxipride.

In the RI patients there was a larger decrease in CLu/F than expected based on their renal function. To compare renal and nonrenal (metabolic) unbound clearance, the bioavailability has to be known. Previous studies showed a high oral bioavailability of remoxipride (> 0.90) with a small variability (Grind *et al.*, 1989; Movin-Osswald & Hammarlund-Udenaes, 1991). Using a value of 0.90 we estimated a marked decrease in the metabolic unbound clearance of remoxipride in RI patients to about 50%. The excretion of unchanged remoxipride in the RI group was 8.4% compared with an expected value of 3%, which argues against a decreased bioavailability and supports a decrease in metabolic clearance. This observation, together with similar Vu/F values in groups, suggests that a decreased metabolism is more likely than a change in bioavailability.

Patients with decreased renal function had significantly increased plasma α_1-acid glycoprotein concentrations. Their unbound volume/bioavailability was unchanged, whereas metabolic unbound clearance was decreased in the renally diseased patients. The mechanism of this decrease remains unclear. Brown *et al.* (1988) suggested that α_1-acid glycoprotein might be a factor in the decrease of the unbound metabolic clearance for disopyramide in renally impaired patients. Accumulation of P450 inhibitors in the plasma of the uraemic patient leading to a decreased metabolic clearance as suggested by Bianchetti *et al.* (1976) might be another explanation.

Steady state plasma concentrations of remoxipride and its metabolites should be reached within 5 days in patients with severely decreased renal function owing to their prolonged half-times, as compared with within 2.5 days for patients with normal renal function. The accumulation ratio of remoxipride and metabolites at steady state will be up to 2 times higher in RI patients as compared with C patients. The accumulation ratio of the metabolites was 3.3 in RI patients compared to 2.0 in C patients.

Although the AUC_u of remoxipride in renally impaired patients was found to be twice that of control patients and the AUC values of some of the metabolites were up to 7 times those in control patients, no adverse events were recorded in any of these patients. However, these differences need to be more carefully assessed under steady state conditions.

Based on the pharmacokinetics of unchanged drug, it is reasonable to suggest that patients with a CL_{Cr} below 25 ml min^{-1} should start treatment with a maintenance dose of remoxipride which is half the normal dose with adjustments thereafter if needed, under careful supervision.

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