HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol. Clin. Exp. **13**, 357–365 (1998)

Mirtazapine Oral Single Dose Kinetics in Patients with Different Degrees of Renal Failure

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To investigate pharmacokinetic parameters, as well as safety of mirtazapine in patients with renal failure, an open-labelled, single oral dose study was performed in normal healthy controls and in patients with mild, moderate and severe renal failure, as distinguished by glomerular filtration rates (GRFs) of Cr-EDTA (values corrected per 1·73 m^2 body surface area). Each group comprised of 10 volunteers (5 males and 5 females). The results show that after a single oral morning dose of 15 mg of mirtazapine, the area under the curve (AUC) for the plasma concentration of this racemic compound was increased in patients with moderate (GFR 22 ± 6 ml/min) and severe (GFR 2 ± 5 ml/min) renal failure compared to controls. The AUCs were, however, unaffected by mild renal failure (GFRs 61 ± 14 ml/min). The oral clearance was found to be lower in patients with moderate or severe renal failure, as well as in females compared to males irrespective of degree of renal failure. The magnitude of renal failure was found not to influence the elimination half-life of mirtazapine (overall mean $\pm$ SD $= 36{\cdot}3 \pm 8{\cdot}1$ h). The adverse experiences (AEs) were reported with similar incidences in all groups, and described as being mild or moderate in nature. The most commonly reported AEs were somnolence and tiredness occurring in one half and one third of the subjects, respectively. The single morning 15 mg/day dose of mirtazapine was well tolerated by patients with renal failure, irrespective of degree of severity. Further research is needed to evaluate repeated dose pharmacokinetics and tolerability of mirtazapine in patients with renal failure. An additional option to optimize treatment of an individual, medically compromised patient is to apply Therapeutic Drug Monitoring (TDM) routines for dose adjustments. Such a pharmacokinetic postmarketing surveillance program is currently under development for mirtazapine.

KEY WORDS — renal failure; antidepressant drugs; mirtazapine; pharmacokinetics; therapeutic drug monitoring (TDM)

INTRODUCTION

Concurrent somatic diseases may occur in patients suffering from psychiatric illnesses. Patients suffering from renal or hepatic impairment will in this respect cause specific problems, since these organs usually play a role in drug metabolism and/or elimination. Therefore, scrutiny on drug kinetic features in these clinically important subpopulations of patients is always highly justified. Moreover, as renal function diminishes by normal aging to about half of that of 20 years of age at the age of 80 years (Epstein, 1995), any impact of renal impairment on drug kinetics will possibly not only occur in patients with renal impairment, but perhaps also in elderly patients in general. Consequently, in elderly patients dosage adjustments may be necessary for certain drugs. With the advent of less toxic psychoactive drugs, it can be envisaged that elderly, as well as those with comorbid medical illness, will become more commonly subjected in the future to longer periods of drug maintenance treatment for a variety of psychiatric disorder. Thus, insufficient knowledge on the possible effect of varying degrees of renal function in drug kinetics may hamper definition of possible different optimal dosing strategies in the different kinds of patients occurring in the naturalistic patient setting. Conceptually, both inter-individual as well as longitudinal intra-individual dose optimization of psychoactive drugs will in part necessitate a better delineation of drug

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CCC 0885–6222/98/050357–09$17·50

kinetics in relation to different degrees of renal impairment. In this context it should be noted that the knowledge on the pharmacokinetics of the most widely used antidepressants in different degrees of renal impairment at present is still far from complete (Hale, 1993).

Mirtazapine (1,2,3,4,10,14b-hexahydro-2-methylpyrazino [2,1-a-]-pyrido[2,3-c][2] benzazepine is an antidepressant with a novel mode of action. Due to enhancement of both the noradrenergic and serotonergic 5-HT_{1A} mediated neurotransmission, mirtazapine is described as a Noradrenergic and Specific Serotonergic Antidepressant (NaSSA) (de Montigny *et al.*, 1995; de Boer *et al.*, 1995). The clinical efficacy and tolerability in the treatment of depression has been verified for both in- and outpatients (for review, see Davis and Wilde, 1996). Orally administered mirtazapine from commercially available Remeron tablets attains an absolute bioavailability of approximately 56 per cent, similar after both single and multiple dosing of 15 mg once daily (Voortman and Paanakker, 1995). A dose proportionality plasma concentration at steady state following 15–75 mg once daily administration of mirtazapine in healthy young male volunteers has also been evidenced (Timmer *et al.*, 1995). Further, the available pharmacokinetic data in healthy volunteers have shown that elimination half-life of mirtazapine was similar after both single and repeated dosing: in young males around 22 h, in young females around 36 h, in elderly males around 31 h, and in elderly females around 40 h (Timmer *et al.*, 1996). Mirtazapine is extensively metabolized in the body with a peak plasma concentration appearing at about 90 min in young males (Delbressine and Vos, 1997).

The pharmacokinetic profile of a single oral dose of mirtazapine, 15 mg/day, administered to normal males and females as well as to patients with mild, moderate and severe renal impairment, as defined by their glomerular filtration rate (GRF), was investigated in an open-labelled study. The aim was to determine pharmacokinetic parameters (peak concentration (C_{max}); time of C_{max} occurrence (t_{max}); elimination half-life ($t_{\frac{1}{2}}$); area under the curve (AUC) for plasma level versus time; and oral clearance corrected for body weight (CL_0), as well as tolerability/safety of this single dose challenge of mirtazapine. Enrolment of both males and females made it possible to further investigate the effect of gender on the single oral dose kinetics of mirtazapine simultaneously with the renal impairment. Based on these objectives we also aimed at addressing the possible significance of our findings in a broader clinical context.

MATERIALS AND METHODS

The clinical part of the study was conducted at Guy's Drug Research Unit, London, UK, after obtaining approval from the responsible ethics committee and regulatory authority. Written informed consent was obtained from all participating subjects prior to the start of the study, which was conducted according to Declaration of Helsinki and later revisions.

Study population

A total of 40 subjects (20 males and 20 females) aged between 39 and 69 years and meeting the inclusion and exclusion criteria were enroled and completed the study. Each subject participated in an active phase (apart from the screening procedure) lasting for 10 consecutive days.

A requirement for all patients with renal impairment was that their renal function was proven to be reasonably stable over a 4 month period preceding the study. If patients were on dialysis, this procedure should have been stabilized for at least 4 months prior to the study. A history of a major psychiatric condition in the last 2 years, seizure disorders, major ECG abnormalities or abnormal laboratory parameters, except those expected in relation to renal insufficiency or related conditions, were strict exclusion criteria. No regular drug intake in the month prior to the study, except for that required for the present renal or related conditions, or abuse of drugs or psychoactive substances (verified by urine screening) within 4 months prior to the study were allowed.

Four groups, each consisting of 5 males and 5 females, were differentiated on the basis of GFR (measured as ml/min by means of ^{51}Cr-EDTA clearance, and corrected for 1·73 m^2 body surface area) defined within 3 months of study baseline:

- Group I: normal healthy controls (GFR $\geqslant$80 ml/min).
- Group II: patients with mild renal insufficiency (GFR 40–79 ml/min).
- Group III: patients with moderate renal insufficiency (GFR 11–39 ml/min).
- Group IV: patients with severe renal insufficiency (GFR $\leqslant$ 10 ml/min).

It should be noted that in group IV there were clinically quite different states of renal failure as evidenced by the variance in the actual GRFs of 2 ± 5 ml/min. Five patients in group IV were on continuous ambulatory peritoneal dialysis, and two patients were on intermittent haemodialysis. Due to the technical reasons, 38 subjects were found eligible for pharmacokinetic evaluation in this study, but all 40 subjects were evaluated for tolerability/safety. Further details of the study population are shown in Table 1.

Table 1. Demographic characteristics and GRFs (measured as ml/min by means of ^{51}Cr-EDTA clearance, and corrected for 1·73 m^2 body surface area) baseline

	Group I Normal healthy controls (GFR $\geqslant$80 ml/min)			Group II Mild renal insufficiency (GFR 40–79 ml/min)			Group III Moderate renal insufficiency (GFR 11–39 ml/min)			Group IV Severe renal insufficiency (GFR $\leqslant$10 ml/min)		
	Male	Female	Whole group	Male	Female	Whole group	Male	Female	Whole group	Male	Female	Whole group
Number of subjects	5	5	10	5	5	10	4	4	8	5	5	10
Age (years, means ± SDs)	51 ± 8	51 ± 4	51 ± 6	52 ± 5	51 ± 9	52 ± 7	59 ± 5	50 ± 10	54 ± 9	58 ± 9	59 ± 7	59 ± 8
Weight (kg, means ± SDs)	78 ± 13	69 ± 6	74 ± 10	80 ± 17	70 ± 9	75 ± 14	76 ± 7	63 ± 14	69 ± 12	76 ± 17	64 ± 12	70 ± 15
Height (cm, means ± SDs)	176 ± 10	164 ± 5	170 ± 10	170 ± 7	167 ± 7	169 ± 7	174 ± 9	158 ± 4	166 ± 11	173 ± 7	163 ± 5	168 ± 8
GFR (ml/min, means ± SDs)	89 ± 8	110 ± 18	100 ± 17	63 ± 13	59 ± 16	61 ± 14	23 ± 6	22 ± 8	22 ± 6	3 ± 6	1 ± 5	2 ± 5

Study design

In this open-label, active medication, parallel group study, a single oral morning dose of 15 mg mirtazapine (Batch No. CP087064, N.V. Organon, Oss, The Netherlands) was taken at 08·00 on day 1 in the fasting state (i.e. nil by mouth since 23·00 on the day before ingesting tablet, denoted as day 0) with a liberal amount of water. On day 0, subjects were hospitalized in the morning at the study centre, where standard meals (taking into account the patient's diet) were provided. Food and drink intake was prohibited until 3 h after the tablet ingestion. Thereafter, meals matching individual diet and meal frequency prior to entering the study were served at regular intervals during the rest of the active phase of the study. Alcohol, caffeine or CO_2 containing beverages were not allowed for 24 h prior to the intake of study drug or during the subsequent active study period. Subjects remained at the study location unit from day 0 until after the 120 h (day 5) blood sampling (see below) for study drug analysis was performed. Subjects were to return to the study location on days 6 (144 h post dosing), 7 (168 h post dosing) and 10 (240 h post dosing), respectively, for the final blood sampling procedures. Discharge from the study occurred after 10 consecutive days of active participation, excluding the screening part of the study.

Blood sampling procedure and mirtazapine plasma analytical methodology

Blood samples were taken at the following times after ingestion of the single oral dose of 15 mg mirtazapine on day 1 of the study: 0 h (pre dose), 15 min, 30 min, 45 min, 1 h, 1 h 30 min, 2 h, 3 h, 4 h, 6 h, 8 h, 11 h, 15 h, 24 h, 36 h, 48 h, 60 h, 72 h, 84 h, 96 h, 108 h, 120 h, 144 h, 168 h and 240 h. Plasma was separated from blood by centrifugation, frozen and stored at 20°C until

analysis was performed. The plasma concentrations of mirtazapine were determined by applying a capillary gas liquid chromatography (GC-LC) method (Data on file, NV Organon, Oss, The Netherlands). In brief, following n-hexane extraction from alkalinized plasma, a gas chromatographic procedure with nitrogen-sensitive detection was used to determine the racemic mirtazapine plasma content in the samples. In each series of analyses on authentic plasma samples, spiked duplicate plasma calibration standards were determined ranging from 0·2 to 50 ng/ml of racemic mirtazapine, as well as including three quality control samples with mirtazapine concentrations of 1, 10 and 40 ng/ml plasma, respectively.

Pharmacokinetic analysis

The following pharmacokinetic parameters were calculated.

C_{max}. The peak concentration (C_{max}) and the time of its occurrence relative to time of ingesting mirtazapine (t_{max}) were taken from the measured plasma levels.

$t_{\frac{1}{2}}$. From individual log-concentration versus time plots by visual inspection of the curves at the linear part of the terminal elimination phase (up to the last sampling time, ideally obtained at day 10 of the study) the concept of elimination half-life was assessed. Applying log-linear regression on the terminal data points, the elimination half-life ($t_{\frac{1}{2}}$) for each individual subject was estimated.

$AUC_{0-\infty}$. The $AUC_{0-\infty}$ (area under curve from zero to infinity) was calculated as the sum of the AUC from zero to the last sampling time on day 10 (or on the last time after dosing at which plasma concentrations could be measured), designated as AUC_{0-t} (calculated by means of the linear trapezoidal rule) and the AUC from the last sampling time to infinity, designated $AUC_{t-\infty}$ (calculated by dividing the fitted concentration of the last sampling time by the terminal slope of the plasma level versus time curve). The fitted concentration at the last sampling time, as well as the terminal slope of the plasma level versus time curve, were obtained from the previously estimated value of the $t_{\frac{1}{2}}$.

CL_0. The oral mirtazapine clearance was calculated by dividing the dose (15 mg) by the $AUC_{0-\infty}$. In order to reduce erroneous inter-subject variability, this CL_0 was further divided by the individual body weights.

Safety assessments

Physical examinations were conducted on screening day (i.e. before day 0 when subjects were hospitalized at the study location) and on day 5. During the hospitalization part of the study (from day 0 to day 5) plus once daily at days 6, 7 and 10, body temperature, sitting blood pressure and heart rate were recorded. A 12-lead resting electrocardiogram (ECG) was performed during the screening procedure and on days 0 and 5 (the latter at the discretion of the investigator). Routine laboratory measurements were performed on screening and days 0 and 5, including blood biochemistry, haematology and urine analysis (as applicable according to the study protocol). The laboratory variables and vital signs were recorded also at discharge from the study at day 10. In addition, all the above mentioned safety assessments were performed during the study at the discretion of the investigator whenever deemed necessary. Adverse experiences (AEs) were recorded both by subjective reporting and active questioning at all visits when blood sampling occurred (see above).

Statistics

All values are expressed as means $\pm$ standard deviations (SDs). Analysis of variance (ANOVA) was performed on log-transformed values since pharmacokinetic parameters most often follow a log-normal distribution. In order to ascertain the validity of this procedure, the different sets of data were first subjected to a test for homogeneity of variance (Fmax-test, Winer, 1971) for the 'subject within group $\times$ sex' term. For parameters where homogeneity was found, a two-way ANOVA (Winer, 1971) was applied. For parameters where no homogeneity was found a non-parametric test, a two-way ANOVA on the rank numbers, was applied. For the CL_0 versus GFR a correlation analysis was conducted, including calculations of the Spearman correlation coefficient. Differences were defined as significant if tail probabilities (p-values) from the appropriate tests were $\leqslant 5\%$ ($p \leqslant 0{\cdot}05$). In all cases when ANOVA F-test showed p-values ranging from $p > 0{\cdot}05$ to $\leqslant 0{\cdot}10$, contrast tests were applied to determine possible differences between the groups in more detail. All

calculations were done using the SAS System Version 6·06 (SAS Institute Inc., Cary, NC, USA; *SAS User Guide 1989*) running under the VAS/VMS Operating System V5·4 on a DEC/VAX computer.

RESULTS

Pharmacokinetic parameters

C_{max}. A statistically significant group effect ($p \leqslant 0{\cdot}05$) was found for the log-transformed C_{max} values. Following the contrast testing, a higher C_{max} was shown for group IV than for groups I and II. No significant gender effect was found, but, particularly between the males, the intersubject variance was large (Table 2).

t_{max}. No statistically significant overall effects between the four groups or between males and females were found (Table 2).

$t_{1/2}$. No statistically significant effects were found for this parameter between the groups or sexes. However, examination by contrast test displayed possible differences between group IV and groups I and II. (Table 3).

$AUC_{0-\infty}$. A statistically significant group but not gender effect was found, with $AUC_{0-\infty}$ in groups III and IV higher than in groups I and II, and in group IV higher than in group III (Table 3).

CL_0. Statistically significant group as well as gender effects were found for CL_0. Groups III

Table 2. The peak concentration (C_{max}; ng/ml) and the time of its occurrence relative to time (t_{max}; hours) following administration of a single oral dose of 15 mg mirtazapine. For statistical evaluation see Results

	C_{max}; ng/ml (means ± SDs)			
	Group I	Group II	Group III	Group IV*†
Males	42·5 ± 16·3	37·3 ± 14·7	53·4 ± 33·0	65·0 ± 45·4
Females	24·7 ± 6·9	26·3 ± 7·8	43·5 ± 19·3	55·0 ± 24·8
Total	33·6 ± 15·1	31·8 ± 12·5	48·5 ± 25·6	60·0 ± 34·9
	t_{max}; hours (means ± SDs)			
	Group I	Group II	Group III*†	Group IV*†‡
Males	1·2 ± 0·3	1·4 ± 0·2	1·0 ± 0·4	1·8 ± 1·4
Females	1·8 ± 0·8	1·5 ± 0·4	1·6 ± 0·5	1·3 ± 1·0
Total	1·5 ± 0·6	1·5 ± 0·3	1·3 ± 0·5	1·5 ± 1·2

*$p \leqslant 0{\cdot}05$, vs Group I. †$p \leqslant 0{\cdot}05$, vs Group II. ‡$p \leqslant 0{\cdot}05$, vs Group III.

Table 3. The terminal elimination half-life ($t_{\frac{1}{2}}$; hours) and $AUC_{0-\infty}$ ($ng \times h^{-1} \times ml^{-1}$). For statistical evaluation see Results

	$t_{1/2}$; hours (means ± SDs)			
	Group I	Group II	Group III	Group IV
Males	28·6 ± 4·7	34·5 ± 6·5	33·6 ± 6·4	42·0 ± 11·4
Females	36·9 ± 6·2	34·0 ± 6·2	38·3 ± 2·4	42·1 ± 11·2
Total	32·8 ± 6·7	34·2 ± 6·0	36·0 ± 5·2	42·1 ± 10·7
	$AUC_{0-\infty}$, $ng \times h^{-1} \times ml^{-1}$ (means ± SDs)			
	Group I	Group II	Group III	Group IV
Males	362 ± 65·9	432 ± 165	618 ± 220	919 ± 352
Females	397 ± 218	349 ± 108	551 ± 5·0	719 ± 84·1
Total	380 ± 153	390 ± 139	584 ± 149	819 ± 263

and IV displayed an overall lower CL_0 than groups I and II, and males displayed a lower clearance than females (Figure 1). The oral clearance from a single dose of 15 mg mirtazapine was estimated to be approximately 30 per cent higher for females in comparison to males, independently of the individual degree of renal impairment. Moreover, a regression analysis showed a positive correlation between CL_0 and GFR for all individuals (Figure 2).

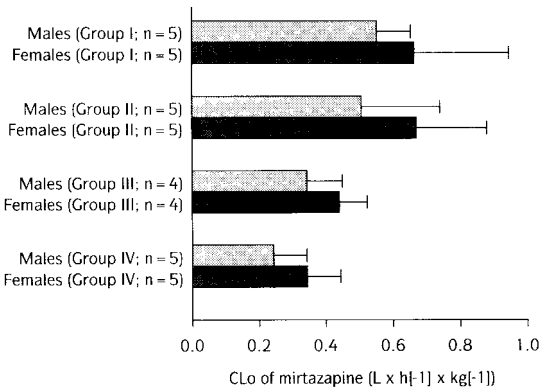

Figure 1. The mirtazapine oral clearance (CL_0, means $\pm$ SDs) in groups I–IV (males: open bars; females: closed bars). For statistical evaluation see Results

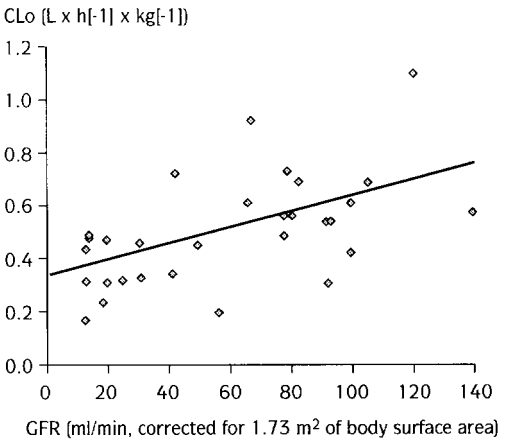

Figure 2. Regression analysis between CL_0 and GFR for all individuals in the study

Safety evaluations

A single oral dose of 15 mg mirtazapine was equally well tolerated by renally impaired patients as by healthy controls. Thirty-seven out of 40 subjects reported AEs; 83 per cent of AEs were described as being mild, 17 per cent as moderate, and only one case of severe drowsiness was reported during the study. The most commonly reported AE were somnolence (20 subjects), tiredness (11 subjects), headache (11 subjects) and dizziness (8 subjects). Blood pressure and heart rate fluctuated during the study, but no clear-cut racemic mirtazapine kinetic-related trends were observed. Hypertension was occasionally recorded in some subjects with renal impairment, but in these cases it was likely the result of the prevailing kidney disease. There were no major and/or clinically relevant changes in ECG recordings and laboratory parameters. In summary, in this study there were no indications or more severe or more frequent AEs in patients with renal impairment compared to healthy controls.

DISCUSSION

It can be envisaged that in patients where renal dysfunction appears concomitantly with major depression of a severity that clearly requires the use of an antidepressant drug, the risk of enhanced drug-related side-effects and toxicity may confound its adequate use. Less toxic and usually better tolerated novel classes of antidepressants are thus likely to be used more readily in patients with concomitant kidney diseases. It should be noted that doses of all efficacious drugs, including antidepressants, usually are best defined on a highly selected, often quite young, medically healthy male population. On the other hand, most of the depressed patients are middle-aged or elderly females. Moreover, a risk for both pharmacodynamic and pharmacokinetic interactions increases with any given comorbidity. In addition, in many cases with elderly patients and, for example, those with concomitant kidney disease, a polypharmacy with risks for drug–drug interaction are at hand. It is, therefore, essential to outline the basic pharmacokinetic features in females, elderly and in co-morbid states before any meaningful interpretation of causality related to drug effects/adverse events in the complex naturalistic clinical setting. In spite of this fact, the current knowledge on the pharmacokinetic profiles of antidepressants in the renally impaired patients is clearly insufficient (Hale, 1993).

The results of pharmacokinetic studies of tricyclic antidepressants (TCAs) in renally impaired patients give equivocal results (Dawling *et al.*, 1982; Sandoz *et al.*, 1984; Lieberman *et al.*, 1985, 1986; Tasset *et al.*, 1985; Dengen *et al.*, 1993). For

example, amitriptyline blood concentrations have been shown to be increased as well as decreased in conjunction with renal failure. In the former case, the higher amitriptyline blood levels in kidney disease were found to correlate with more pronounced adverse effects than normally observed after a single oral dose (Dengen *et al*., 1993), a phenomenon not seen in the latter case (Sandoz *et al*., 1984). Overall though, there seems to be an agreement concerning altered metabolism of many TCAs in renal failure, resulting in the cumulating of either parent compound (Lieberman *et al*., 1985, 1986; Dengen *et al*., 1993) or unconjugated and/or conjugated metabolites of the different TCAs that have been investigated (Dawling *et al*., 1992; Sandoz *et al*., 1984; Lieberman *et al*., 1985, 1986; Dengen *et al*., 1993). The clinical significance of this observation as of today could be to acknowledge the importance of applying Therapeutic Drug Monitoring (TDM) for avoiding toxic blood levels of TCAs (Preskorn and Fast, 1991; Preskorn, 1993), especially in patients with comorbid conditions such as renal failure. It should be noted that in this condition, in addition to the parent compound, potentially toxic metabolites of the drug may also cumulate (Young, 1991). Fluoxetine appears to be best investigated drug in renally impaired patients among newer antidepressants, with pharmacokinetics and pharmacodynamics studied following both single and repeated doses (Aronoff *et al*., 1984; Bergstrom *et al*., 1991, 1993). Neither the rate nor the extent of accumulation of plasma fluoxetine or norfluoxetine concentrations differed between patients with severe renal impairment requiring chronic haemodialysis and patients with normal kidney function when a dose of 20 mg/day was given for more than 2 months. This may suggest that renal function is not a major factor to consider when dosing fluoxetine. However, tolerability of fluoxetine was not discussed (Bergstrom *et al*., 1993). Since both fluoxetine and norfluoxetine are strong inhibitors of CYP2D6 and are racemic in nature, a possibility of adverse reactions on a kinetic basis still exists in this group of patients and thus has to be further investigated. Data on fluvoxamine (Hale, 1993; Data on File, Kali Duphar Laboratories, Worthington, Ohio, 1986) showed no influence of the drug on renal function assessed by serial renal function test following a 6-week open label study with 100 mg/day of fluvoxamine. However, the clearance of fluvoxamine has not been assessed and 7 out of 25 patients discontinued prematurely due to gastrointestinal intolerance. For paroxetine, results of only a single oral 30 mg dose study have been reported showing a kinetic aberration in renal impairment affecting plasma levels of paroxetine and reducing the elimination $t_{\frac{1}{2}}$ of the drug (Doyle *et al*., 1988). As high first-pass metabolism of paroxetine renders usually less than 2 per cent of a given dose to be found in urine, these results could be interpreted as rather unexpected. A single oral dose of sertraline was given to two anuric haemodialysis patients (Schwenk *et al*., 1995). The results showed that absorption and distribution of sertraline were not altered compared to historic controls with normal renal function, whereas the elimination $t_{\frac{1}{2}}$ was prolonged implying an impaired clearance of sertraline in renally impaired subjects. The lack of dialysability for sertraline was interpreted by the authors that in case of a lower dose of sertraline given to patients in haemodialysis, no further compensatory administration is necessary after dialysis (Schwenk *et al*., 1995). This finding could also be interpreted to be that haemodialysis is probably of no use in patients acutely or chronically overdosed with sertraline. Concerning citalopram, the most commonly used selective serotonin reuptake inhibitor (SSRI) in the Nordic countries, no data other than an abstract have been found in the literature relating to patients with renal failure (Joffe *et al*., 1993).

In a single case report concerning trazodone, it is concluded that perhaps the focus in renally impaired subjects should not be on the parent compound kinetics but rather on its metabolites, as this drug is extensively metabolized in humans (Doweiko *et al*., 1984). The only available reversible monoamine oxidase inhibitor, moclobemide, has been administered both orally and intravenously in two single dose studies to patients with varying degrees of renal impairment (Schoerlin *et al*., 1990; Stoeckel *et al*., 1990). No major changes were found in kinetic or disposition parameters of moclobemide in patients with renal impairment compared to historic controls. A reduced elimination of the N-oxide metabolite, normally excreted to 6–10 per cent in urine, is, however, likely to be present in patients with a clinically significant decrease in creatinine clearance (Schoerlin *et al*., 1990). As there is a clear tendency to use moclobemide in high doses (i.e. $\geqslant$900 mg/day) in clinical practice today, the risk of cumulating moclobemide and/or its metabolites should be further evaluated in renally

impaired patients to justify safety of these high doses. Venlafaxine, and its metabolite *O*-desmethylvenlafaxine (ODV) have been studied using a single oral 50 mg/dose in subjects with varying degrees of renal impairment (Troy *et al*., 1994). The oral clearance of both venlafaxine and ODV decreased by approximately 55 per cent, accompanied a significantly prolonged terminal elimination $t_{\frac{1}{2}}$ in the most severely impaired patients treated by haemodialysis. Therefore, a dose adjustment of venlafaxine is warranted for patients with creatinine clearance <30 ml/min (Troy *et al*., 1994). These findings also indicate a need for further studies with repeated doses of venlafaxine, assessing also the tolerability and safety of the drug. Moreover, the use of TDM-routines for venlafaxine/ODV when dosing this drug to patients with renal failure should clearly be advocated at present.

The results of the actual study with a single oral dose of 15 mg mirtazapine show that the C_{max} and the AUC are increased, and, consequently, CL_0 is decreased in patients with moderate or severe renal failure. Since in the present study elimination $t_{\frac{1}{2}}$ was not found to be overtly changed, the observed decrease in CL_0 could possibly be related to a decrease in the volume of distribution and/or to an increase in the bioavailability. However, on the basis of the single oral dose pharmacokinetics study, it is at the present stage impossible to discern which of these two kinetic parameters (or both) contribute to the observed change in CL_0 of mirtazapine in patients with moderate or severe renal failure. This issue may be elucidated in a study with repeated dosing of the drug to renally impaired subjects, which should also include an intravenous dose of mirtazapine. In addition, the CL_0 was also found to be about 30 per cent higher in females compared to males, irrespective of the level of the renal dysfunction. Demographic data of patients in the present study show that among healthy controls the males had a lower average GFR than the females. This type of observed difference in GFR between the sexes or investigated groups of subjects is not frequently presented in reports from clinical trials. In addition, in the present study the variance in the C_{max} values was found to be more pronounced for males in all groups compared to females. Overall, though, the main kinetic parameters obtained in this study are in agreement with those in healthy volunteers from a previous study by Timmer and colleagues (1996), including the higher oral clearance in females. Finally, a single dose 15 mg of mirtazapine was found to be well tolerated in a similar manner by patients with varying degrees of renal impairment and by healthy controls. The repeated safety parameters measurements and adverse effects recording during the present study adhered to standard protocol procedures for psychoactive drugs. Although the dose of 15 mg/day in the renally impaired subjects resulted in generally more drug exposure (increased AUC and decreased CL_0) than in the healthy controls, there were no differences in reported adverse effects between the groups. In summary, a single oral dose of 15 mg of mirtazapine administered to severely renally impaired patients (with mean GFR of 2 ± 5 ml/min) is considered to be safe, although further investigation of pharmacokinetic parameters upon repeated dosing in renally impaired patients and/or influence of, for example, gender should be performed. In the meantime a TDM-based program is under development at the Department of Clinical Pharmacology, Lund University, Sweden. This project will be initiated to follow-up these pertinent issues of current posology for mirtazapine in the naturalistic clinical setting.

ACKNOWLEDGEMENT

The authors gratefully acknowledge T. Mant, MD, for participation in the data collection part of this study. This study was supported by a grant from NV Organon, Oss, The Netherlands.

REFERENCES

Aronoff, G. R., Bergstrom, R. F., Pottratz, S. T., Sloan, R. S., Wolen, R. L. and Lemberger, L. (1984). Fluoxetine kinetics and protein binding in normal and impaired renal function. *Clinical Pharmacology and Therapeutics*, **36**, 138–144.

Bergstrom, R. F., Beasley, C. M. Jr., Levy, N. B., Blumenfield, M. and Lemberger, L. (1991). Fluoxetine pharmacokinetics after daily doses of 20 mg fluoxetine in patients with severely impaired renal function. *Pharmaceutical Research*, **8**, S294.

Bergstrom, R. F., Beasley, C. M. Jr., Levy, N. B., Blumenfield, M. and Lemberger, L. (1993). The effects of renal and hepatic disease on the pharmacokinetics, renal tolerance, and risk-benefit profile of fluoxetine. *International Clinical Psychopharmacology*, **8**, 261–266.

de Boer, T., Ruigt, G. S. F. and Berendsen, H. H. G. (1995). The apha2-selective adrenoceptor anatagonist

Org 3770 (Mirtazapine, Remeron®) enhances noradrenergic and serotonergic transmission. *Human Psychopharmacology*, **10**, S107–S118.

Davis, R. and Wilde, M. I. (1996). Mirtazapine. A review of its pharmacology and therapeutic potential in the management of major depression. *CNS Drugs*, **5**, 389–402.

Dawling, S., Lynn, K., Rosser, R. and Braithwaite, R. (1982). Nortriptyline metabolism in chronic renal failure: metabolite elimination. *Clinical Pharmacology and Therapeutics*, **32**, 322–329.

Delbressine, L. P. C. and Vos, R. M. E. (1997). The clinical relevance of preclinical data: mirtazapine, a model compound. *Journal of Clinical Psychopharmacology*, **17**, 29S–34S.

Dengen, J., Wolke, E., Seiberling, M., Pintar, P., Hoxer, G., Steinhauer, H. B. and Fischer, W. (1993). Vergleichende Untersuchung zur Pharmakokinetik von Amitrptylinoxid und Trimipramin nach Einmalgabe bei gesunden manlichen Probanden und Patienten mit Niereninsuffizienz. *Mediziniche Klinik*, **88**, 129–133.

Doweiko, J., Fogel, B. S. and Goldberg, R. J. (1984). Trazodone and hemodialysis (letter). *Journal of Clinical Psychiatry*, **45**, 361.

Doyle, G. D., Laher, M., Kelly, J. G., Byrne, M. M., Clarkson, A. and Zussman, B. D. (1988). The pharmacokinetics of paroxetine in renal impairment. *Acta Psychiatrica Scandinavica*, **80**, S89–S90.

Epstein, M. (Ed.) (1995). *The Kidney in Liver Disease*. Hanley and Belfus, Philadelphia.

Hale, A. S. (1993). New antidepressants: use in high-risk patients. *Journal of Clinical Psychiatry*, **54**, S61–S70.

Joffe, P., Lyby, K., Jørgensen, T. and Hellstrøm, B. (1993). The kinetics of citalopram in renal failure. *Journal of the American Society of Nephrology*, **4**, S251.

Lieberman, J. A., Cooper, T. B., Suckow, R. F., Steinberg, H., Borenstein, M., Brenner, R. and Kane, J. M. (1985). Tricyclic antidepressant and metabolite levels in chronic renal failure. *Clinical Pharmacology and Therapeutics*, **37**, 301–307.

Lieberman, J. A., Cooper, T. B., Suckow, R. F., Steinberg, H., Borenstein, M. and Brenner, R. (1986). Tricyclic antidepressant drug and metabolite levels in chronic renal failure. *Annals of the New York Academy of Sciences*, **463**, 304–306.

de Montigny, C., Haddjeri, N., Mongeau, R. and Blier, P. (1995). The effects of mirtazapine on the interactions between central noradrenergic and serotonergic systems. *CNS Drugs*, **4**, S13–S17.

Preskorn, S. H. (1993). Pharmacokinetics of antidepressants: why and how they are relevant to treatment. *Journal of Clinical Psychiatry*, **54**, S14–S34.

Preskorn, S. H. and Fast, C. A. (1991). Therapeutic drug monitoring for antidepressants: efficacy, safety and cost-effectiveness. *Journal of Clinical Psychiatry*, **52**(6), 23–30.

Sandoz, M., Vandel, S., Vandel, B., Bonin, B., Hory, B., St Hillier, Y. and Volmat, R. (1984). Metabolism of amitriptyline in patients with chronic renal failure. *European Journal of Clinical Pharmacology*, **26**, 227–232.

Schoerlin, M.-P., Horber, F. F., Frey, F. J. and Mayersohn, M. (1990). Disposition kinetics of moclobemide, a new MAO-A inhibitor, in subjects with impaired renal function. *Journal of Clinical Pharmacology*, **30**, 272–284.

Schwenk, M. H., Verga, M. A. and Wagner, J. D. (1995). Hemodialyzability of sertraline. *Clinical Nephrology*, **44**, 121–124.

Stoeckel, K., Pfefen, J. P., Mayersohn, M., Schoerlin, M.-P., Anderssen, C., Ohnhaus, E. E., Frey, F. J. and Guentert, T. W. (1990). Absorption and disposition of moclobemide in patients with advanced age or reduced liver or kidney function. *Acta Psychiatrica Scandinavica*, **82**, S94–S97.

Tasset, J. J., Singh, S. and Pesce, A. J. (1985). Evaluation of amitriptyline pharmacokinetics during peritoneal dialysis. *Therapeutic Drug Monitoring*, **7**, 255–257.

Timmer, C. J., Lohmann, A. A. M. and Mink, C. P. A. (1995). Pharmacokinetic dose-proportionality at steady state of mirtazapine from Remeron tablets. *Human Psychopharmacology*, **10**, S97–S106.

Timmer, C. J., Paanakker, J. E. and Van Hal, H. M. J. (1996). Pharmacokinetics from orally administered tablets: influence of gender, age, and treatment regimen. *Human Psychopharmacology*, **11**, 497–509.

Troy, S. M., Schultz, R. W., Parker, V. D., Chiang, S. T. and Blum, R. A. (1994). The effect of renal disease on the disposition of venlafaxine. *Clinical Pharmacology and Therapeutics*, **56**, 14–21.

Voortman, G. and Paanakker, J. E. (1995). Bioavailability of mirtazapine from Remeron® tablets after single and multiple oral dosing. *Human Psychopharmacology*, **10**, S83–S96.

Winer, B. J. (1971). *Statistical Principles in Experimental Design*. McGraw-Hill, New York.

Young, R. C. (1991). Hydroxylated metabolites of antidepressants. *Psychopharmacology Bulletin*, **27**, 521–532.

