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MIRTAZAPINE PHARMACOKINETICS IN HEALTHY THAI VOLUNTEERS

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ABSTRACT

Mirtazapine (MZP) is a third-generation antidepressant with a dual mode of action. To investigate the pharmacokinetic profile of MZP in 22 healthy Thai volunteers (12 males, 10 females), each volunteer received a single 30mg oral dose of MZP in the form of conventional tablets, in the fasting state. Serial blood samples were taken and MZP plasma concentrations were measured from 0 to 72 h by a HPLC-UV spectrometry validated method. Pharmacokinetic parameters were calculated and statistically analyzed from MZP plasma levels.

Means ± standard deviations of the pharmacokinetic parameters were as follows: The rate of absorption, as measured by peak level (C_{max}) and peak time (t_{max}) were 169.9 ± 31.5 ng ml^{-1} and 0.6 ± 0.2 h, respectively. The extent of absorption, as measured by area under the curve from zero time to the last measurable sampling time (AUC_{0-last}), and total area under the curve from time zero to infinity (AUC_{0-inf}), were 564.4 ± 241.6 ng ml^{-1} h and 678.6 ± 283.9 ng ml^{-1} h, respectively. Elimination rate, characterized by termination half-life ($t_{1/2}$), was 10.4 ± 5.6 h.

A comparison with published pharmacokinetic studies on MZP demonstrated a significantly greater absorption rate and elimination in Thai subjects. Meanwhile, the total extent of absorption (AUC_{0-inf}) of MZP was not different (p>0.05).

Key words: pharmacokinetic, antidepressant, NaSSA, HPLC, absorption, elimination, half-life

INTRODUCTION

Mirtazapine (MZP), a novel tetracyclic antidepressant, belonging to the piperazino-azepine group of compounds, is not related to any known class of psychotropic drugs. MZP is the first noradrenergic and specific serotonergic antidepressant ('NaSSA'). It has a unique pharmacological profile combining dual action on both noradrenergic and serotonergic neurotransmitter systems with a specific action on particular serotonergic receptor subtypes (Timmer et al., 2000). MZP has only a weak affinity for 5-HT1 receptors and has very weak muscarinic anticholinergic and histamine (H1) antagonist properties. As a consequence of its unique pharmacodynamic properties, MZP oral administration has been shown to be effective,

safe and well-tolerated in the treatment of depressed patients (Fawcett and Barkin, 1998). The efficacy of MZP was superior to placebo (Bremner, 1995; Clagborn and Lessern, 1995; Sitsen et al., 1995; Kahn, 1995) or trazodone (Van Moffaert et al., 1995). MZP showed equivalent efficacy to commonly used tricyclic antidepressants such as amitriptyline (Bremner, 1995; Sitsen et al., 1995; Mullin et al., 1997; Zivkov and De Jongh, 1995), clomipramine (Richou, 1995) and doxepin (Marttilla, 1995). In all these active controlled studies, MZP had a more favorable side effect profile than the comparator drugs. MZP was also found to be efficacious in the treatment of elderly depressed patients (Halikas, 1995; Hoyberg, 1997).

MZP is rapidly and well absorbed from the gastrointestinal tract after single and multiple oral administrations, and peak plasma concentrations are reached within 2 hours. The presence of food has a minor effect on the rate, but does not affect the extent, of absorption. The absolute bioavailability is approximately 50%, mainly because of gut wall and hepatic first-pass metabolism. The elimination half-life of MZP ranges from 20 to 40 hours (26 hours in males, 37 hours in females); longer half-lives, up to 65 hours, have occasionally been recorded and shorter half-lives have been seen in young males. The elimination half-life is sufficient to justify once-a-day dosing. MZP binds to plasma proteins (85%) in a nonspecific and reversible way. MZP displays linear pharmacokinetics over a dose range of 15 to 80 mg (Timmer et al., 1995; 2000; Voortman and Paanakker, 1995).

MZP is extensively metabolized in the liver to four metabolites via demethylation and hydroxylation, followed by glucuronide conjugation. The unconjugated desmethyl metabolite is pharmacologically less active than the parent compound. MZP lacks auto-induction of hepatic isoenzymes. Although MZP is a substrate of P450 isoenzymes 1A2, 2D6 and 3A4, it is not a potent inhibitor or inducer of any of these enzymes (Fawcett and Barkin, 1998). The pharmacokinetics of MZP appears to be enantioselective, resulting in a higher plasma concentration and longer half-life of the (R)-(-)-enantiomer (18.0 +/-2.5 h) compared with that of the (S)-(+)-enantiomer (9.9+/-3.l h) (Timmer et al., 2000).

Genetic CYP2D6 polymorphism has different effects on the enantiomers. For the (R)-(-)-enantiomer, there are no differences between poor (PM) and extensive (EM) metabolizers of debrisoquine [a cytochrome P450 (CYP) 2D6 substrate] for any of the kinetic parameters; for (S)-(+)-mirtazapine, the area under the concentration-time curve (AUC) is 79% larger in PM than in EM, and a corresponding longer half-life was found. However, there were no clinically or statistically significant differences between poor (PM) and extensive (EM) metabolizers of debrisoquine [a cytochrome P450 (CYP) 2D6 substrate] with regard to the pharmacokinetics of the racemate (Timmer et al., 2000).

In addition, the pharmacokinetics of MZP are dependent on gender and age: females and the elderly show higher plasma concentrations than males and young adults. As a consequence, statistically significant effects of gender and age were observed. The differences, however, were not large enough to justify any dose adjustments (Timmer et al., 2000). There is no clinical information available regarding the effect of race on the pharmacokinetics of MZP. By the way, the actions of the body on an administered MZP in Thai people have not been evaluated. In this paper we present the results of the first study to assess the pharmacokinetic profile of MZP in healthy Thai volunteers.

MATERIALS AND METHODS

1. Materials

MZP reference standard from Sigma-Aldrich, USA. (Lot No. 017K4715) was used in the analytical assay. The pharmaceutical formulation of 30 mg MZP conventional tablets (Remeron®, Batch No.:806173/805927) were manufactured by N.V. Organon, Oss, The Netherlands. The internal standard was carbamazepine (USP™, CAT. No. 09300J, USP Rockville, MD).

2. Sample preparation

The MZP and internal standard were extracted from plasma samples by the following process. Pipetted 1 ml plasma sample into a 15 ml screw cap tube. A 10 µL of 10 µg/L carbamazepine (internal standard) in methanol was subsequently added to plasma in each tube then mixed by vortex. Add 200 µL of 2 M NaOH for basified then homogenized by vortex mixer for 1 minute. Added 3 ml of ethyl acetate and vortexed for 1 min. Each tube was centrifuged at 2500 rpm at room temperature (25 ℃) for 10 min. A portion of 1000 µL of the supernatant (organic layer) was evaporated to dryness under a stream of nitrogen gas at 40 ℃. The residue was reconstituted with 100 µL of methanol : mobile phase (1:1) before injected into the HPLC.

3. Analytical procedures

All plasma samples were analyzed for MZP concentration using a HPLC method with UV detection (HPLC-UV; Agilent Technology 1100 Series, Germany, with DAD UV detector) at the Laboratory Center for Food and Agriculture Products Co., Ltd. (Chiang Mai),

Thailand. The UV absorbance detection of MZP and the internal standard (carbamazepine) was performed at the wavelength of 290 nm. The injection volume of treated plasma sample was 20 µL. A gradient mixture of methanol (40% to 80% in 10 min):water acidified with 20 uL trifluoroacetic acid per liter (60% to 20 % in 10 min) was used as mobile phase. It was pumped at 1.0 ml/min through the column (Zorbax C18 SB Agilent Technologies, USA, 150 mm x 4.6 mm). The peak area was measured and the peak area ratio of the drug to the internal standard and the concentration were calculated.

Assay methodology and validation for analysis method was performed before using for the determination of plasma MZP concentration. All plasma samples were analyzed for MZP concentration according to a sensitive, selective, and accurate HPLC method with UV detection (HPLC-UV). Assay validation was done by determination of specificity, linearity, limit of quantification, accuracy, precision and stability.

The calibration points were 3, 10, 20, 50, 150, 200 and 300 ng of MZP per ml of plasma, with a fixed (30 ng) amount of internal standard. Quality control plasma samples (in triplicate) were 5, 100, and 250 ng of MZP per ml of plasma, spiked with 100 ng of internal standard.

A series of analyses was accepted as correct under the following conditions: (i) the calibration curve contained at least 10 calibration points; (ii) the correlation coefficient exceeded 0.9900; (iii) the back calculated levels of the calibration samples did not deviate more than ± 15% from the nominal concentration at the lower limit of quantification (3 ng/ml) of MZP, and not more than ± 15% for all other concentrations; and (iv) the accuracy (% difference from nominal concentration) and the precision (coefficient of variation) for the quality control samples did not exceed 15% for all concentrations

4. Ethical clearance and consent

The study protocol was approved by the Ethical Review Committee for Research in Human Subjects, Ministry of Public Health, Thailand. All volunteers gave written informed consent before enrolling in the study. The study was performed at Suanprung Psychiatric Hospital, Chiang Mai Province.

5. Subjects

The twenty two volunteers were healthy Thai males and females. All of them fulfilled screening and inclusion and exclusion criteria including blood pressure, pulse rate, body temperature, and respiratory rate. Clinical laboratory analyses including hemoglobin, hematocrit, total white blood cell(WBC) count, differential WBC count, serum creatinine, blood urea, serum AST, serum ALT, alkaline phosphatase, bilirubin, and urine. They gave written informed consent before enrolling in the study. Screening included a complete medical history, physical examination including vital signs and clinical laboratory evaluation. Subjects were included if physical and laboratory test results were normal. Inclusion also required that subjects refrained from smoking within 1 week prior to, and during the study.

Subjects were excluded for any of the following reasons: known hypersensitivity to MZP, clinical significant cardiovascular, renal, hepatic, endocrine, metabolic, pulmonary or hematological disease. Subjects also were excluded if they consumed caffeine or alcohol within 72 hours prior to initiation of the study, or had any other clinical condition that could affect the absorption, distribution, biotransformation or excretion of MZP.

6. Experimental design

This was an open-label, active medication study with a single dose. No blinding procedures were used. After overnight fasting, each subject was assigned to be administered one Remeron® 30mg tablet orally with 200 ml of water under medical supervision. Blood samples were collected at each sampling time. The subjects were allowed to have normal activities while avoiding physical exertion. Food and water were allowed 4 h post-dose.

7. Blood sample collection

A catheter was inserted into a forearm vein for blood sample collection and flushed after each blood drawn with heparinised saline solution. Blood (6 ml) was drawn from antecubital veins through the injection plug and collected into coded polyethylene tubes containing sodium heparin as an anticoagulant. There were 16 blood samples collected, i.e. before dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 36, 48 and 72 hours after drug administration. They were

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centrifuged immediately to separate plasma from blood cell within half an hour and stored in Pyrex® glass tube at -70ºC until analysis for MZP content.

8. Subject monitoring

During the trial, volunteers resided at the trial sites. All volunteers were monitored for temperature, blood pressure and radial pulse prior to MZP administration and at 1, 4, 8, 12, 24, 48 h post-dose. Safety and tolerability were evaluated from reported adverse events. All adverse events were recorded from either spontaneous subject reports or by investigator observation. Severity and relationship to the study drug were noted for each adverse event.

On completion of the study or early withdrawal, subjects had a post complete physical examination within 7 days of the last blood sample collection.

9. Pharmacokinetic parameters and statistical analysis

Pharmacokinetic data were analyzed using noncompartmental methods. Plasma concentration-time curves were plotted. Pharmacokinetic parameters were derived from measures of concentration using Microsoft Excel software. The rate of absorption was estimated by the peak plasma concentration after MZP administration (C_{max}; ng/ml) and time to reach peak plasma concentration (t_{max}; h). The C_{max} and t_{max} were obtained directly from the visual inspection of the plasma concentration-time curves. The apparent elimination rate constant (k_e) was calculated by the linear regression of the log-transformed concentrations of the drug in the terminal portion of the concentration vs. time profile. The half-life ($t_{1/2}$) of the terminal elimination phase was obtained using the relationship $t_{1/2} = 0.693/ k_e$.

The extent of product bioavailability is estimated by the area under the plasma concentration vs time curve (AUC). The AUC from time zero to the last sampling time (AUC_{0-last}; ng. h/ml) was calculated by using the linear trapezoidal rule. The total extent of absorption (AUC_{0-inf}; ng.h/ml) was determined by adding the extrapolation of these areas to infinity (AUC_{t-inf}), value C_{last}/k_e, to the calculated AUC_{0-last} (where C_{last} = the last detectable concentration; k_e = the elimination rate constant).

Clearance, a descriptive term used to evaluate efficiency of drug removal from the body, is not an indicator of how much drug is being removed. It only represents the theoretical volume of blood which is totally cleared of drug per unit time. The apparent plasma clearance (CL/F) was determined as Dose/AUC_{0-inf} and apparent volume of distribution (V_d/F) calculated as Dose / (k_e * AUC_{0-inf}).

10. Statistical analyses

Only the data from subjects who completed the study was included in the statistical analysis. All estimated pharmacokinetic parameters were summarized with descriptive statistics. The primary parameters of interest for the statistical analysis were C_{max}, t_{max}, $t_{1/2}$, AUC_{0-last}, AUC_{0-inf}, ke, CL and V_d of MZP. The differences of these parameters between gender were tested by Two-sample Kolmogorov-Smirnov Test at p value<0.05.

In the comparison of main parameters from this study vs previous studies were conducted using One-Sample t-test, if One-Sample Kolmogorov-Smirnov Test revealed normal distribution.

RESULTS

1. Demographic data

Twenty two healthy subjects, 12 males and 10 females, fulfilled inclusion and exclusion criteria. All of them entered the study and completed it. Demographic data on the volunteers are given in Table 1. No significant differences in age and body mass index (BMI) were found between genders (p>0.05, using Mann-Whitney U Test).

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Table 1 *Demographic data of subjects*

		Sex		Total	P
		Male (n=12)	Female (n=10)	(n=22)	value*
Age (years)	Average	27.8	27.5	27.7	0.628
	sd.	5.8	7.4	6.4	
	Range	21-41	21-43	21-43	
Body mass index (kg/m²)	Average	22.91	21.67	22.1	0.314
	sd.	1.62	2.57	2.1	
	Range	18.73-24.80	18.44-24.97	18.44-24.97	

* Mann-Whitney U Test between genders

2. Pharmacokinetic parameters

Linear and semi-log plot of the MZP mean plasma concentrations versus time over the 24-h truncated sampling period (Figure 1 and Figure 2) illustrated first order elimination kinetics of MZP. Drug concentration-time profiles showed that the medication was well absorbed from the gastrointestinal tract following oral administration and MZP was already measurable at the first sampling time (0.5 h) in all volunteers with t_{max} ranging from 0.5 to 1.0 h. The last measurable time point was found to be 24 h. From the plasma level versus time curves, it was found that the terminal log-linear part started at 4 h after dosing, so that the interval from 4 h up to the last sampling point was used for the estimation of the elimination half-life.
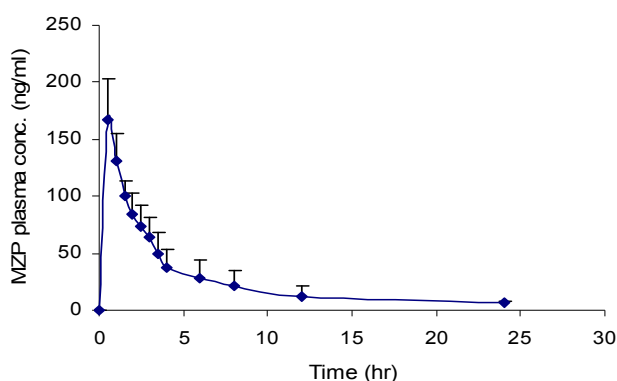

Figure 1 *Linear plot of average (standard deviation) plasma concentration-time curve of mirtazapine after a single oral dose of 30 mg of mirtazapine(MZP) conventional tablets (Remeron®) in 22 healthy Thai volunteers.*
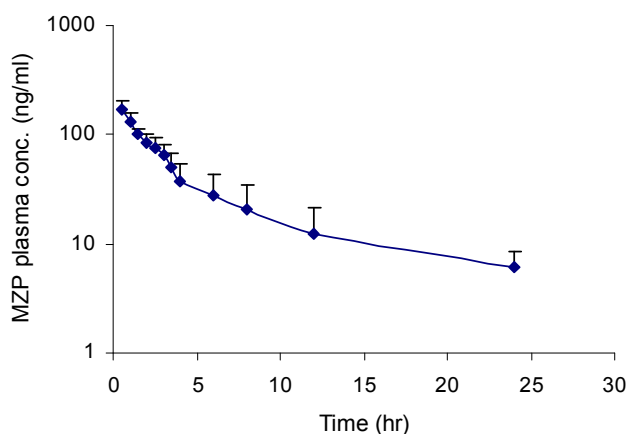

Figure 2: *Semi-log plot of average (standard deviation) plasma mirtazapine concentration at various sampling times in healthy Thai volunteers. (n=22).*

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Following oral single dose of 30mg MZP conventional tablet, a summary of the pharmacokinetic parameters as mean and standard deviation (sd) were shown in Table 2. The

published parameters from previous studies which used the same dose and formulation were selected for comparison and also presented in Table 2.

Table 2: *Average (sd.) and comparison of pharmacokinetic parameters in this study versus previous published studies.*

Parameters	Present study			Previous published studies			
	Average	sd.	Range	Average	sd.	Reference[c]	P value*
C_{max}	169.9	31.5	111.2-237.9	69.7	17.5	1	<0.05
(ng/ml)				80.6	-	2	<0.05
				81.6	38.4	3	<0.05
AUC_{0-last}	564.4	241.6	308.1-1167.1	589	142	4	0.637
(ng.hr/ml)				652	30	2	0.104
				710	256	3	0.010
AUC_{0-inf}	678.6	283.9	327.5-1341.1	760	299	3	0.193
(ng.hr/ml)				705	-	2	0.667
$t_{1/2}$ (hr)	10.4	5.6	4.02-23.49	21.5	5	4	<0.05
				27.8	NA	2	<0.05
				25.8	9.3	3	<0.05
t_{max} (h)	0.6	0.2	0.5-1	1.8	1.4	3	[a]
				1.0	NA	2	[a]
CL (L/h)	50.6	17.6	19.9-81.5	31.2	4.3	5	<0.05
V_d (L)	646.27	195.67	371-1030	339	125	5[b]	<0.05
k_e (h^{-1})	0.088	0.047	0.0295-0.1286	NA	NA	-	-

Independent T-Test for normal distribution data; k_e : Elimination constant
NA : Data not available; V_d : Apparent volume of distribution;   CL : Apparent plasma clearance
[a] : non-normal distribution, statistical analysis could not be carried out
[b] : volume of distribution at steady state
[c] : References are:

1. Spaans et al. 2002;
2. Organon Canada Ltd., Product Monograph Remeron RD[TM], Dec 16, 2004;
3. Organon Inc, Original NDA: 21-208. Submission data, 2000;
4. Timmer et al., 1997;
5. Voortman and Paanakker, 1995

Significant differences were found in some parameters. Thai volunteers revealed greater C_{max} and peak plasma concentration occurred (t_{max}) more rapidly. Using absorption data from time zero to 24 h (AUC_{0-last}), results are inconsistent. The average AUC_{0-last} published by Timmer and colleagues(1997), of 52 ng.h/ml, and the Product Monograph (Organon Canada Ltd 2004) of 589 ng.h/ml, were greater than but be not significantly different (p>0.05) from the value obtained in this study of 564 ng.h/ml. The AUC_{0-last} value reported in the original NDA: 21-208 submission data (2000) of 710 ng.h/ml, was significantly greater.

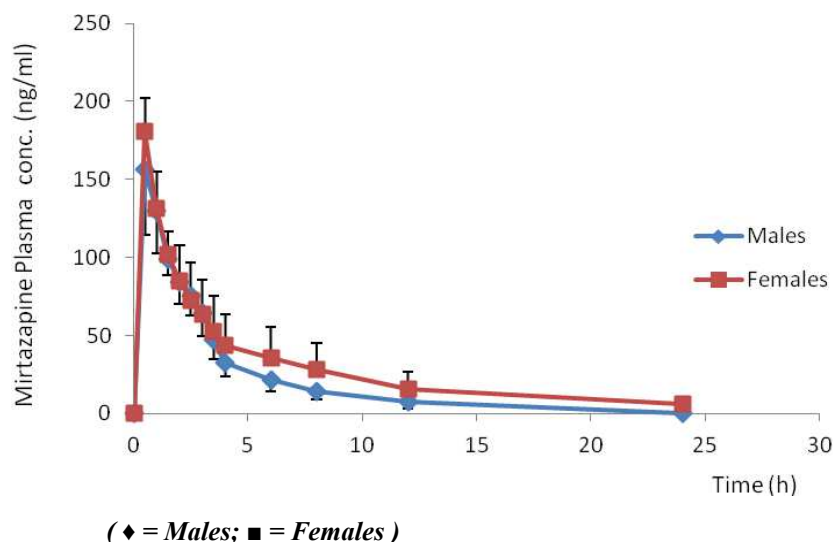The total AUC (AUC_{0-inf}) from all studies showed no significant difference (p>0.05).

Thai volunteers had a higher (p<0.05) apparent volume of distribution (V_d) of 646 L, and apparent plasma clearance (CL) of 17.6 L/h. The elimination half-life ($t_{1/2}$) demonstrated in this study was significantly shorter.

The average ± sd. of pharmacokinetic parameters separated into gender subgroup were summarized in Table 3 and Figure 3. There was a statistical difference (p<0.05) between males and females in AUC_{0-last}, k_e and $t_{1/2}$. Significant differences in C_{max}, t_{max} , CL, Vd and AUC_{0-inf} between genders were not found (p>0.05).

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Table 3 : *Pharmacokinetic parameters of volunteers after taking a Remeron® 30mg tablet.*

	Males		Females		All subjects		P value*
	Average	sd.	Average	sd.	Average	sd.	
C_{max} (ng/ml)	160.6	36.4	181.1	21.2	169.9	31.5	0.107
t_{max} (h)	0.6	0.2	0.5	0.0	0.6	0.2	0.346
AUC_{0-last} (ng.h/ml)	456.6	79.2	693.7	307.4	564.4	241.6	0.030
AUC_{0-inf} (ng.h/ml)	565.3	169.5	814.5	339.5	678.6	283.9	0.056
CL (L/h)	58.1	16.9	43.1	15.4	50.6	17.6	0.219
V_d (L)	614.7	186.8	677.8	208.1	646.3	195.7	0.399
k_e (h^{-1})	0.110	0.051	0.062	0.026	0.088	0.047	0.015
$t_{1/2}$	8.1	5.1	13.0	5.1	10.4	5.6	0.015

* Mann-Whitney U Test between genders

(♦ = *Males;* ■ = *Females*)

Figure 3: *Mean and standard deviation concentration-time curves per gender*

DISCUSSIONS

Females showed more a rapid and higher absorption rate than males. The extent of exposure to MZP during the first 24 h was significantly greater in female subjects (693.7 $\pm$ 307.4 ng.h/ml) compared to male subjects (456.6 $\pm$ 79.2 ng.h/ml). Finally, total extent of exposure (AUC0-inf) in females (814.5 $\pm$ 339.5 ng.h/ml) and males (565.3 $\pm$ 169.5 ng.h/ml) was not significant different (p>0.05). Females had larger V_d (677.8 $\pm$ 208.1 L) than males (614.7 $\pm$ 186.8 L) (p>0.05). Females showed lower CL (43.1 $\pm$ 15.4 L/h) than males (58.1 $\pm$ 16.9 L/h). Subsequently, the elimination half-life of MZP in females was significantly longer $t_{1/2}$ (13.0 $\pm$ 5.1 h) than males (8.1 $\pm$ 5.1 h).

1. Rate of Absorption
Following oral administration of mirtazapine in healthy Thai volunteers, higher peak plasma concentrations (C_{max}) were reached in a shorter time period indicating that the rate of absorption in healthy Thai volunteers is more rapid than in previous comparator studies listed in Table 2. (Voortman and Paanakker, 1995; Timmer et al., 1997; 2000; Organon Inc, 2000; Organon Spaans et al., 2002; Canada Ltd., 2004).

Timmer and colleagues (2000) found that the pharmacokinetics of mirtazapine appear to be

enantioselective, resulting in a higher plasma concentration and longer half-life of the (R)-(-)-enantiomer (18.0 $\pm$ 2.5 h) compared with the (S)-(+)-enantiomer (9.9 $\pm$ 3.l h). There were no clinically or statistically significant differences between poor (PM) and extensive (EM) metabolizers of debrisoquine [a cytochrome P450 (CYP) 2D6 substrate] with regard to the pharmacokinetics of the racemate.

The MZP use in this study (Remeron®) is a racemic mixture of the (R)-(-)-enantiomer and the (S)-(+)-enantiomer as in previous studies. Additionally, the MZP plasma analysis was measured in terms of the total of both enantiomers. Therefore isomeric differences cannot account for the difference in findings in this study. Moreover, Timmer and colleagues (2000) found that the low absolute bioavailability of MZP depended on gut wall and hepatic first-pass metabolism. Therefore, the rapid and greater absorption rate of MZP in Thai subjects, characterized by about a 2 times higher C_{max} and 2-3 times shorter $t_{1/2}$, is probably a result of lesser first-pass metabolism in the gut wall and liver. The clinical effect of the differences in the MZP absorption rate in Thai patients warrants further study.

2. Extent of Absorption

The extent of absorption of MZP was measured by the area under the plasma level versus time curve, AUC_{0-last} and AUC_{0-inf} . Though, there was conflict in the significant difference of the initial extent of absorption (AUC0-last) in some studies. Total extent of absorption (AUC_{0-inf}) found to be not significant different between the present and previous studies (Timmer et al., 1997; 2000; Organon Inc, 2000; Organon Canada Ltd., 2004). However, all previous published AUC parameters seemed to be larger than in this study. These results may be due to faster metabolism in Thai subjects, confirmed by a significantly higher body clearance.

3. Elimination half-life

The elimination of MZP is measured by its elimination half-life. The half-life found in this study (mean 10.4 $\pm$ 5.6 h) was significantly shorter than in previous studies (mean 21.5 to 27.8 h). This phenomenon may be due to a higher metabolism and body clearance rate in Thai subjects. If the elimination half-life of MZP

ranges from 20 to 40 hours, the time to reach steady state is about 4 to 6 days (Timmer et al., 2000). Data from this stuy indicates that steady state plasma levels of MZP in Thai subjects may be attained in about 2 to 3 days

Major pathways of biotransformation are demethylation and oxidation followed by conjugation. Cytochrome P450 enzymes 2D6, 1A2 and 3A4 are involved in the formation of mirtazapine metabolites. The pharmacokinetics of MZP appears to be enantioselective, resulting in higher plasma concentrations and a longer half-life of the (R)-(-)-enantiomer compared with that of the (S)-(+)-enantiomer. Genetic CYP2D6 polymorphism has differing effects on the metabolism of the enantiomers. For the (R)-(-)-enantiomer there are no differences between EM and PM for any of the kinetic parameters. For (S)-(+)-mirtazapine the area under the concentration-time curve (AUC) is 79% larger in poor metabolizer than in extensive metabolizer, and a corresponding longer half-life was found (Timmer et al., 2000). The significant difference in t1/2 found in this study indicates that the effects of genetic polymorphism on the MZP kinetic parameters in Thai people warrants further study.

4. Gender

The pharmacokinetics of MZP appear to be gender dependent. Females exhibited significantly longer elimination half-lives than males (mean half-life of 13.0 hours for females vs. 8.1 hours for males). The elimination half-life of MZP reported in previous studies was 37 hours for females and 26 hours for males (Timmer et al., 2000).

CONCLUSION

This pharmacokinetic study in healthy Thai volunteers reveals that MZP is rapidly and completely absorbed following oral administration and has a half-life of about 10 hours. Peak plasma concentrations are reached in about 0.5-1 hours. This is markedly different from pharmacokinetic results reported in previous studies and may have an effect on clinical outcomes. Further study on the pharmacokinetics of MZP and pharacogenomic effects in Thai patients is warranted.

REFERENCES

1. Bremner JD. A double-blind comparison of Org 3770, amitriptyline and placebo in major depression. J. Clin. Psychiatry. 1995; 56:519-525.
2. Clagborn JL, Lessern MD. A double-blind placebo controlled study of Org 3770 in depressed outpatients. J. Affect. Disord. 1995; 34:165-171.
3. Fawcett J, Barkin RL. Review of the results from clinical studies on the efficacy, safety and tolerability of mirtazapine for the treatment of patients with major depression. J Affect Disord. 1998 Dec; 51(3):267-85.
4. Gorman JM. Mirtazapine: Clinical overview. J Clin Psychiatry. 1999; 60 Suppl 17:9-13.
5. Halikas JA. Org 3770 (mirtazapine) versus trazodone: a placebo controlled trial in depressed elderly patients. Hum. Psychopharmacol. 1995;10 (SuppI2): SI25-SI33.
6. Hoyberg OJ, Maragakis B, Mullin J, Norum D, Stordall E, Ekdahl P, Ose E, Moksnes KM, Sennef C. A double-blind multicentre comparison of mirtazapine and amitriptyline in elderly depressed patients. Acta Psychiatrica Scandinavica. 1996;93(3):184–190.
7. Kahn MC. A randomized, double-blind, placebo-controlled, 5-weeks' study of Org 3770 (mirtazapine) in major depression. Hum. Psychopharmacol. 1995;10(Suppl 2):S119-S124.
8. Marttilla M, Jaaskelainen J, Jarvi R, et al. A double-blind study comparing the efficacy and tolerability of mirtazapine and doxepin in patients with major depression. Eur. Neuropsychopharmacol. 1995; 5:441-446.
9. Mullin J, Lodge A, Bennie E, McCreadie R, Bhatt GS, Fenton G. A multicentre, double-blind, amitriptyline-controlled study of mirtazapine in patients with major depression. J. Psychopharmacol. 1996;10:235–240.
10. Organon Inc. Remeron (mirtazapine) tablets prescribing information. West Orange, NJ. 2005 Jun.
11. Original NDA: 21-208. Organon Inc, Submission data, 4/28/2000.
12. Product Monograph Remeron RD^{TM}, Organon Canada Ltd., Control Number 093844, Dec 16, 2004.
13. Product Monograph, ^{PR}Remeron RD^{TM}, (mirtazapine) Orally disintegreting tablets 15, 30,45 mg Antidepressant. Organon Canada Ltd. Control Number 093844, Dec 16, 2004.
14. Richou H, Ruimy P, Charbaut J, et al. A multicentre, double-blind, c1omipramine-controlled efficacy and safety study of Org 3770. Hum Psychopharmacol. 1995;10:263-271.
15. Sitsen JMA, Zivkov M, Dieterle D. Wirksamkeit under Verträglichkeit von Org 3770 bei Patienten mit einer. Major depression. Psychopharmakotherapie 1995; 52:68-71.
16. Spaans E, van den Heuvel MW, Schnabel PG, Peeters PAM, Ching-kon-Sung UG, Colbers EPH, Sitsen J. Concomitant use of mirtazapine and phenytoin: A drug-drug interaction study in healthy male subjects. Eur J Clin Pharmacol. 2002;58:423-9.
17. Timmer CJ, Lohmann A, Mink CPA. Pharmacokinetic dose-proportionality study at steady state of mirtazapine from Remeron tablets. Hum. Psychopharmacol.1995;10(Suppl 2): S97-SI06.
18. Timmer CJ, Paanaker JE, Vrijmed-de-Vries M. Mirtazapine pharmacokinetics with two
19. dosage regimens and two pharmaceutical formulations. Pharm. Res. 1997;14:98–102.

20. Timmer CJ, Sitsen JM, Delbressine LP. Clinical pharmacokinetics of mirtazapine. Clin Pharmacokinet. 2000 Jun;38(6):461-74.

21. Van Moffaert M, De Wilde J, Vereecken A, Dierick M, Evrarad JL, Wilmotte and Mendlewicz J. Mirtazapine is more effective than trazodone. A controlled study in hospitalised patients with major depression. Int Clin Psychopharmacol. 1995;10:3-9.

22. Voortman G, Paanakker J E. Bioavailability of mirtazapine from Remeron® tablets after single and multiple oral dosing. Hum Psychopharmacol. 1995;10(Suppl 2):S83–S96.

23. Zivkov M, De Jongh G. Org 3770 vs amitriptyline: a 6-week, randomized double-blind multicentre trial in hospitalized depressed patients. Hum Psychopharmacol. 1995;10:173-180.

24. Zivkov M, Roes KCB, Pols AG. Efficacy of Org 3770 (mirtazapine) vs amitriptyline in patients with major depressive disorder: a meta-analysis. Hum Psychopharmacol. 1995;10(Suppl 2): S135-S145.