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Research Article

Impact of CYP1A2 induction on pharmacokinetics of melatonin

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ABSTRACT

Melatonin, a hormone secreted by the pineal gland, regulates circadian rhythm and has been investigated for therapeutic use in conditions linked to altered melatonin levels. However, pharmacokinetic data in the Thai population are limited, and interindividual variability may be influenced by CYP1A2 activity. This study evaluated the pharmacokinetics of melatonin and the effect of CYP1A2 induction in 25 healthy Thai male volunteers. The study was conducted in two phases: a baseline phase to characterize melatonin pharmacokinetics under normal conditions, and a postinduction CYP1A2 induction with 120 mg/day omeprazole for 7 days. An *in vivo* CYP1A2 activity was assessed using the saliva paraxanthine/caffeine (PX/CA) ratio. In both phases, a single oral dose of 20 mg melatonin was administered, and blood samples were collected at 0, 0.25, 0.5, 1.0, 1.25, 1.5, 2, 3, 4, 5 and 6 hrs post-dose. Plasma melatonin concentrations were quantified using an HPLC-fluorescence technique. Results from the baseline phase showed rapid absorption with a mean maximum concentration (C_{max}) of 53.42 ± 49.52 ng/mL, a total area under the curve ($AUC_{0\text{-}inf}$) of 63.10 ± 53.15 ng·h/mL, an apparent clearance (Cl/F) of 8.08 ± 5.23 L/hr·kg, and an elimination half-life (T1/2) of 0.80 ± 0.14 hr. Following omeprazole treatment, the saliva PX/CA ratio increased by approximately 1.77-fold, indicating enhanced *in vivo* CYP1A2 activity. Concomitantly, both the C_{max} and $AUC_{0\text{-}inf}$ of melatonin decreased by approximately twofold, to 26.33 ± 34.83 ng/mL and 30.29 ± 28.10 ng·h/mL. In conclusion, CYP1A2 activity appears to play a significant role in modulating bioavailability of melatonin.

Keywords:
Melatonin; Pharmacokinetics; CYP1A2 induction; Bioavailability

1. INTRODUCTION

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone primarily synthesized and secreted by the pineal gland, with tryptophan as its precursor [1,2]. It plays a critical role in regulating the circadian rhythm, particularly the sleep-wake cycle in humans [1,2]. Melatonin secretion follows a distinct diurnal pattern, with peak plasma levels (60-200 pg/mL) occurring during the night and significantly lower levels (0-20 pg/mL) during the day and this rhythmic secretion underscores its importance in maintaining physiological homeostasis [1]. Beyond its role in sleep regulation, melatonin has been implicated in a wide range of health conditions. Reduced melatonin levels have been associated with various diseases, including cancers, neurodegenerative diseases, seizures, depression and autism [2,3,4,5]. Additionally, diminished melatonin levels have been linked to neurodegenerative diseases, seizures, and depression [4,5]. The decline in melatonin levels in modern society has been partly attributed to increased exposure to light at night (LAN), which disrupts its natural secretion [6]. Notably, the International Agency for Research on Cancer (IARC) has classified LAN as a probable carcinogen (Group 2A)[7], further emphasizing the importance of understanding melatonin's role in health and disease.

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Given its broad physiological and therapeutic implications, melatonin has garnered significant attention as a potential treatment for conditions associated with altered melatonin levels. It is widely used as a sleep aid for insomnia and jet lag in many countries, including Thailand. Typical doses for sleep disorders range from 1 to 10 mg daily, while higher doses (10-50 mg daily) have been explored for their potential benefits in cancer treatment, either as monotherapy or as an adjuvant to chemotherapy [3,8,9,10,11]. Studies suggest that melatonin at these doses may improve one-year survival rates, enhance the complete response to chemotherapy, and reduce disease progression and chemotherapy-related side effects such as leukopenia, nausea, vomiting, and thrombocytopenia [12,13].

Melatonin is primarily metabolized in the liver via hydroxylation into 6-hydroxymelatonin, which is subsequently conjugated (sulfonated and glucuronidated) before urinary excretion [14]. The oral bioavailability of melatonin is relatively low (15%) due to significant first-pass metabolism (50-60%) [15,16]. CYP1A2 is recognized as the key enzyme in melatonin metabolism [17]. This enzyme is responsible for metabolizing 5-10% of clinically used drugs and its activity can be induced by various factors, including smoking, char-grilled food, cruciferous vegetables, and medications such as clozapine, olanzapine, carbamazepine, phenobarbital, primidone, rifampin, and omeprazole [18]. Despite CYP1A2 plays critical role in melatonin metabolism, the impact of CYP1A2 induction on melatonin pharmacokinetics remains poorly understood

To date, published data on the pharmacokinetic parameters of melatonin at therapeutic doses are limited, and, to the authors' knowledge, the pharmacokinetics of melatonin in the Thai population have not been investigated. Therefore, this study aims to characterize the pharmacokinetics of melatonin in healthy Thai male volunteers and evaluate the impact of CYP1A2 induction on melatonin pharmacokinetics. The findings will provide essential data for optimizing melatonin dosing and therapeutic outcomes in this population.

2. MATERIALS AND METHODS

2.1. Chemicals

Melatonin, 5-methoxytryptamine, caffeine, paraxanthine and β-hydroxytheophylline were purchased from Sigma-Aldrich Co. LLC., Singapore. All reagents used for the determination of melatonin in plasma were of HPLC grade and obtained from RCI Labscan Limited, Bangkok, Thailand.

2.2. Study population

Twenty-five healthy Thai male volunteers, aged 18–55 years, were enrolled in the study. Volunteers had a body mass index (BMI) ranging from 18 to 25 kg/m² and a minimum body weight of 45 kg. Eligibility was determined based on medical histories, physical examinations, and standard clinical laboratory tests. Exclusion criteria included a history of kidney disease, liver disease, cardiovascular diseases, blood disorders, gastrointestinal disorders, hepatitis, drug abuse, alcoholism, AIDS, or HIV seropositivity. Volunteers who were smokers or ex-smokers (within the past year) or with a history of drug hypersensitivity or adverse reactions to melatonin were also excluded.

The study protocol was approved by the Khon Kaen University Ethics Committee for Human Research (approval number: HE561318). All volunteers were provided with detailed verbal and written information regarding the study objectives and experimental procedures. Written informed consent was obtained from each participant prior to their inclusion in the study.

2.3. Study setting

The study was conducted at Department of Pharmacology, Faculty of Medicine, Khon Kaen University. Throughout the study, participants were closely monitored for adverse drug reactions by trained nurses and physicians. Any adverse events were recorded and managed appropriately.

2.4. Determination of CYP1A2 activity and pharmacokinetic study of melatonin prior to CYP1A2 induction

To assess baseline CYP1A2 activity, saliva samples were collected from each participant. A 2 mL saliva sample was obtained prior to the administration of a caffeine beverage (Nescafe Espresso®, containing approximate 150 mg of caffeine). Subjects were instructed to avoid caffeine-containing products for at least 24 hrs prior to the test. Breakfast was permitted 2 hrs after caffeine intake. At 6 hrs after caffeine administration, a second 2 mL saliva sample was collected to determine the paraxanthine (PX) and caffeine (CA) concentrations by HPLC-fluorescence technique. The saliva PX/CA ratio, which serves as a biomarker for *in vivo* CYP1A2 activity.

Following the baseline CYP1A2 activity assessment, subjects underwent a pharmacokinetic study of melatonin. After an overnight (12-14 hrs) fast, each subject was administered a single 20 mg melatonin capsule (General Drug House Co., Ltd., Bangkok, Thailand) orally with 240 mL of water. Subjects remained in a sitting position for 2 hrs post-administration unless clinically required to change posture. Lunch was provided 4 hrs after melatonin administration. Participants were allowed to engage in normal activities but were instructed to avoid strenuous

physical exertion. Blood samples (approximately 8 mL each) were collected via an indwelling cannula placed in the median cubital vein at the following time points: pre-dose (0 hr) and at 0.25, 0.5, 1.0, 1.25, 1.5, 2, 3, 4, 5, and 6 hrs after melatonin administration. Blood samples were collected into K3EDTA-coated tubes and immediately placed on ice. Plasma was separated by centrifugation at 2,500 rpm for 10 minutes at 4°C. The plasma was aliquoted into pre-labeled tubes and stored at -80°C until analysis.

2.5. Determination of CYP1A2 activity and pharmacokinetic study of melatonin after CYP1A2 induction

After completing the initial melatonin pharmacokinetic study, participants were administered 60 mg of omeprazole (Siam Pharmaceutical Co., Ltd., Bangkok, Thailand) twice daily for 7 days to induce CYP1A2 activity. On day 8 of omeprazole administration, *in vivo* CYP1A2 activity was reassessed using the same saliva PX/CA ratio as described earlier.

2.6. Determinations of paraxanthine and caffeine in saliva

Aliquot of 300 µL of saliva sample was added to a screw capped tube containing 400 mg ammonium sulfate and spiked with 100 µL of 100 µM β-hydroxytheophylline, as internal standard (IS). Saliva samples were then extracted with 3 mL of dichloromethane/isopropanol (85:15, v/v) by vortex mixer at full speed for 1 minute and centrifuged at 2,500 g 15^{o} C for 10 minutes. The organic solvent layer was collected and dried under a nitrogen stream and dissolved in 100 µL of mobile phase before injection of 10 µl into a Nucleosil® C18 column (4x150mm), 4µm particle size (Phenomenex, CA, USA) used at room temperature. The mobile phase consisted of 10 mM ammonium acetate, methanol and tetrahydrofuran (90:8.5:1.5, v/v) at a flow rate 1.2 mL/min. The detection wavelength of ultraviolet detection was set at 276 nm. Under these conditions, the retention times for the paraxanthine, IS and caffeine were 5.9 minutes, 6.8 and 10.7 minutes, respectively.

2.7. Determination of melatonin in plasma

Plasma melatonin concentrations were determined using a validated high-performance liquid chromatography (HPLC) method as previously described [19]. Briefly, 1 mL of plasma was pipetted into a screw-capped tube and spiked with 50 µL of the internal standard, 5-methoxytryptamine (500 ng/mL), and 100 µL of 4 M NaOH solution. The mixture was extracted with 5 mL of dichloromethane by vortexing for 1 minute. The organic phase was separated by centrifugation at 2,091 × g for 10 minutes, transferred to a new tube and evaporated under a stream of nitrogen at 40°C. The residue was reconstituted in 100 µL of HPLC mobile phase by vortexing for 30 seconds and transferred to a vial. A 10 µL aliquot was injected into a Novapak® C18 column (3.9 × 150 mm, 4 µm particle size; Waters, MA, USA) using an autosampler. The mobile phase consisted of 10 mM phosphate buffer and acetonitrile (80:20, v/v) at pH 7.2, with a flow rate of 1.0 mL/min. Detection was performed using a fluorescence detector with excitation and emission wavelengths set at 286 nm and 346 nm, respectively. Under these conditions, the retention times for the internal standard and melatonin were 3.5 minutes and 6.1 minutes, respectively.

2.8. Data and statistical analysis

Plasma melatonin concentrations were calculated using the peak area ratio of melatonin to the internal standard, plotted against a standard curve. Pharmacokinetic parameters were derived using a non-compartmental model with Kinetica 2.0 software (Thermo Fisher Scientific Inc., Waltham, MA, USA). The peak plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) were obtained directly from the observed data. Individual concentration-time profiles were plotted, and the terminal disposition rate constant (Lz) was determined by log-linear regression of at least three data points in the terminal phase. The terminal half-life ($T_{1/2}$) was calculated as 0.693 divided by Lz. The area under the plasma concentration-time curve from time zero to the last measurable concentration (AUC_{0-t}) was calculated using the linear trapezoidal method. Total AUC (AUC_{0-inf}) was determined as AUC_{0-t} + Ct/Lz, where C_t is the last observed concentration. F (oral bioavailability) was absorption fraction after oral administration. All data are expressed as the mean ± standard deviation unless otherwise stated. Prior to analysis, data were examined for normality using the Shapiro–Wilk test. For normally distributed data, comparisons between pre- and post-omeprazole treatment were performed using paired Student's t-tests; when data did not meet normality assumptions, the Wilcoxon signed-rank test was employed. A P-value of less than 0.05 was considered statistically significant.

3. RESULTS

3.1. Demographic characteristics and safety evaluation

A total of twenty-five healthy Thai male volunteers were enrolled in this study. All participants were healthy based on physical examination and blood

chemistry results, as evaluated by a physician. The mean age (± SD) was 22.16 ± 2.08 years, with a mean weight of 64.40 ± 13.64 kg and a mean BMI of 21.15 ± 9.72. Melatonin administration was well tolerated in all subjects, with no serious adverse drug reactions reported. However, ten out of the 25 subjects (40%) experienced drowsiness as the only observed ADR.

3.2. CYP1A2 activity induction by omeprazole

Before and after omeprazole induction, saliva PX/CA ratios of each subject was assessed and used as indexes of CYP1A2 activity. The scatter dot plot of PX/CA ratios before and after CYP1A2 induction with omeprazole of the study population was show in Figure 1. The mean and standard deviation of saliva PX/CA ratio after omeprazole administration was increased from base line (0.62 ± 0.26 to 1.02 ± 0.26) (Figure 1). Result from Pair T-test analysis showed that the mean ratio of PX/CA after induction with omeprazole was significant different when compared with the ratio of the baseline ($p < 0.001$). The mean percentage changed of PX/CA ratio was 77.05 ± 45.62%.

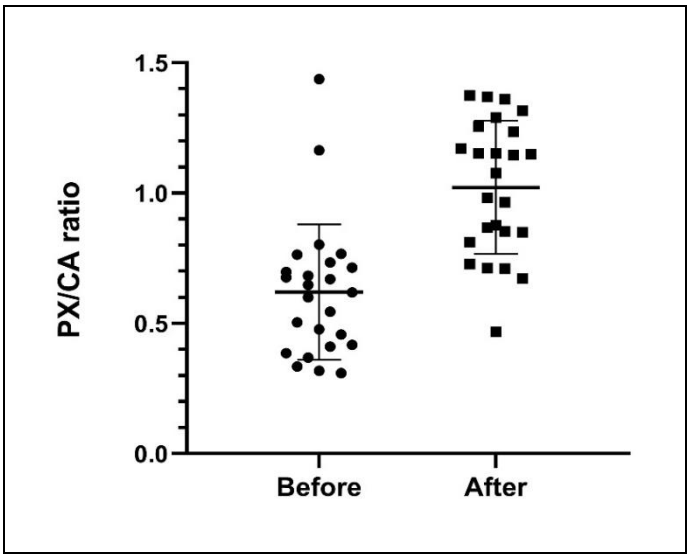

Figure 1. Scatter dot plot of PX/CA ratios before and after CYP1A2 induction with omeprazole.
Note: Each dot represents PX/CA ratio of individual subject. The horizontal line represents the mean value and the vertical line represents standard deviation.

3.3. Comparison of melatonin pharmacokinetic parameters before and after CYP1A2 induction

The mean plasma concentration-time profiles of melatonin and its semi-logarithmic plots before and after CYP1A2 induction are illustrated in Figure 2. The pharmacokinetic parameters of melatonin before CYP1A2 induction in the 25 healthy volunteers were determined using a non-compartmental model (Table 1). Before CYP1A2 induction, the mean maximum plasma concentration (C_{max}) was 53.42 ± 49.52 ng/mL, with a range of 10.33 to 188.19 ng/mL. The median time to reach C_{max} (T_{max}) was 0.62 ± 0.23 hrs. The area under the plasma concentration-time curve from time zero to the last measurable concentration ($AUC_{0\text{-}t}$) was 62.56 ± 52.90 ng·hr/mL, while the total area under the curve ($AUC_{0\text{-}inf}$) was 63.10 ± 53.15 ng·hr/mL. The apparent clearance (Cl/F) of melatonin was high, with a mean value of 8.08 ± 5.23 L/hr·kg. The mean elimination rate constant (Lz/F) was 0.88 ± 0.14 hr^{-1}, corresponding to a terminal half-life ($T_{1/2}$) of 0.81 ± 0.14 hrs. Variation of these pharmacokinetic parameters was noted among individual subjects.

The pharmacokinetic parameters of melatonin after CYP1A2 induction compared with those before omeprazole treatment shown in Table 1. The mean C_{max}, $AUC_{0\text{-}t}$ and AUC_{tot} were significant difference after CYP1A2 induction ($p < 0.01$). The mean C_{max} was decreased about 2-folds (53.42 ± 49.52 to 26.33 ± 34.83 ng/mL) while the mean $AUC_{0\text{-}tlast}$ decreased from 62.56 ± 52.90 to 30.29 ± 28.10 hr·ng/mL and also $AUC_{0\text{-}inf}$ reduced from 63.10 ± 53.15 to 30.86 ± 28.36 hr·ng/mL. Cl/F after induction was increased from 8.08 ± 5.23 to 17.32 ±13.33 L/hr·kg. T_{max} and $T_{1/2}$ were slightly changed without significance differences. CYP1A2 activity increase after induction with omeprazole caused reduction of the C_{max} by 50.71 ± 29.66%, $AUC_{0\text{-}t}$ by 51.58 ± 46.88% and AUC_{tot} by 51.09 ± 46.64%. On the other hand, the Cl/F of melatonin was increased by 114.36 ± 154.88%.

4. DISCUSSION

The present study investigated the pharmacokinetic parameters of melatonin following oral administration of a 20 mg dose in healthy Thai male volunteers, both before and after CYP1A2 induction. To the best of the authors' knowledge, this is the first study to report on the pharmacokinetics of melatonin in a Thai population and the effect of CYP1A2 induction by omeprazole on the pharmacokinetic of melatonin. Notably, there was considerable variability in the C_{max} and AUC values of melatonin among individuals. After administering omeprazole for 7 days, the saliva PX/CA ratio, an indicator of CYP1A2 activity, increased approximately two folds. The pharmacokinetic parameters of melatonin, particularly C_{max} and AUC, were significantly reduced post-omeprazole treatment. This reduction likely results from the induction of *in vivo* CYP1A2 activity, indicating the crucial role of CYP1A2 in the metabolism and oral bioavailability of melatonin.

In the present study, the induction of CYP1A2 by omeprazole was evaluated using the PX/CA concentration ratio [20]. This ratio reflects the conversion of CA into PX which primarily mediated via CYP1A2 [21].

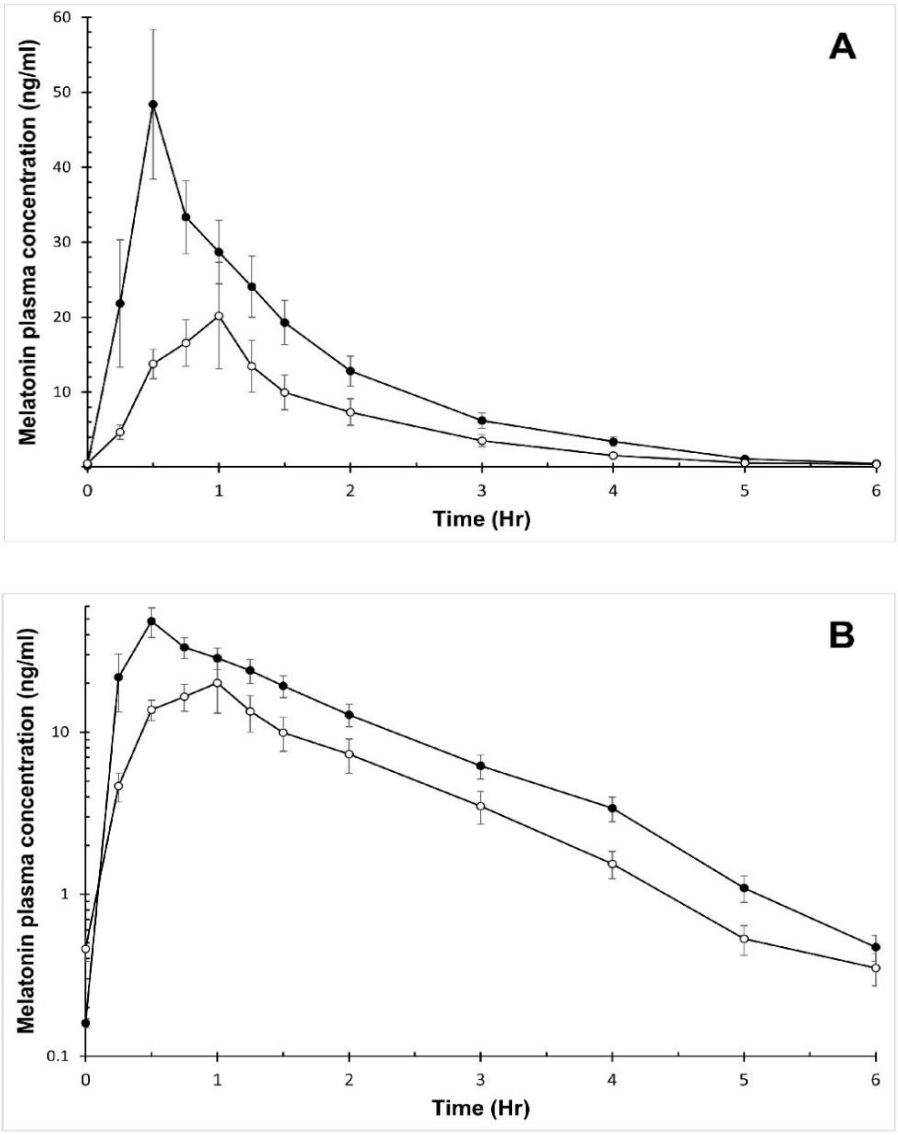

Figure 2. Comparison of mean plasma melatonin concentration-time profiles (**A.)**, semi-log plot of mean plasma melatonin concentration - time profiles **(B)** before and after CYP1A2 induction (±SE); black dot (●) represent before and white dot (○) represent after CYP1A2 induction.

The plasma PX/CA ratio has shown strong correlation with CA clearance and is widely accepted as a measure of *in vivo* clearance of CA [22,23]. Optimal measurement occurs 6 hrs after CA administration [22]. Saliva PX/CA ratio has been demonstrated to be highly correlated with systemic CA clearance and can be used as an *in vivo* index of CYP1A2 activity [24].

Omeprazole is recognized as an inducer of CYP1A2, especially at high doses. Studies have shown that a 120 mg/day dose substantially increases CYP1A2 activity, with urinary CA metabolite concentrations rising by 25-32% between 5-8 hrs, and serum PX/CA ratio increasing by 48% after 7 days [25,26]. However, standard doses of 20-40 mg/day, commonly used in peptic ulcer treatments, do not exhibit significant induction effects [26]. The dose-dependent nature of omeprazole's effects shows significant impact only at the 120 mg/day dosage, enhancing CA clearance by 31.6% [27]. The mechanistic pathway involves activation of the aryl hydrocarbon receptor (AhR) [28]. In the present study, we used omeprazole (60 mg, bid) as a CYP1A2 inducer because, despite the high dose required for induction, it remains within the safe usage range for clinical conditions such as Zollinger–Ellison syndrome [29]. Post-omeprazole treatment, the mean saliva PX/CA ratio increased from 0.62 ± 0.26 to 0.95 ± 0.26, approximately a 1.77-fold increase (range 0.92–3.09). These results indicated that CYP1A2 induction was achieved with 60 mg omeprazole administered twice daily for 7 days and the induction is somewhat higher than earlier reports using urinary PX/CA ratios after 120 mg/day omeprazole therapy [30].

Table 1. Pharmacokinetic parameters of melatonin in healthy Thai male volunteers

Pharmacokinetic parameters	Period of induction	
	Before	After
C_{max} (ng/mL)	53.42 ± 49.52	26.33 ± 34.83*
T_{max} (hr)	0.50 [0.25 – 1.25]	0.75 [0.25 – 1.25]
AUC_{0-t} (ng·hr/mL)	62.56 ± 52.90	30.29 ± 28.10*
AUC_{0-inf} (ng·hr/mL)	63.10 ± 53.15	30.86 ± 28.36*
$T_{1/2}$ (hr)	0.80 ± 0.14	0.81 ± 0.21
Lz/F (hr^{-1})	0.88 ± 0.14	0.92 ± 0.24
Cl/F (L/hr·kg)	8.08 ± 5.23	17.32 ± 13.33*

Notes: Pharmacokinetic parameters shown in arithmetic mean ± SD except for T_{max} shown as median [range]. C_{max}, maximum melatonin plasma concentration; AUC_{0-t}, area under the curve from the dosing time to the last measurable plasma concentration; T_{max}, time of maximum observed concentration; $T_{1/2}$, terminal half-life; Lz/F, apparent elimination rate constant; Cl/F, apparent body clearance; F, oral bioavailability; * $p < 0.05$.

Pharmacokinetic analysis prior to CYP1A2 induction revealed a mean melatonin C_{max} of 53.4 ± 49.5 ng/mL, with AUC_{0-t} of 62.6 ± 52.9 ng·hr/mL and AUC_{0-inf} of 63.1 ± 53.2 ng·hr/mL. The apparent clearance (Cl/F) averaged 8.08 ± 5.23 L/hr·kg, and the half-life ($T_{1/2}$) was 0.81 ± 0.14 hr. These parameters are largely consistent with previous studies conducted in other populations such as Swedes [31] and in premenopausal females [32]. Consistent with previous studies [17], large interindividual variability in the C_{max} and AUC values of melatonin were observed in the present study.

After 7 days of omeprazole treatment, an approximate twofold reduction in melatonin exposure was observed, with the mean plasma C_{max} decreasing from 53.4 ± 49.5 ng/mL to 26.3 ± 34.8 ng/mL and AUC_{0-t} declining from 62.6 ± 52.9 ng·hr/mL to 30.3 ± 28.1 ng·hr/mL (Table 1). Furthermore, Cl/F increased significantly from 8.08 ± 5.23 to 17.3 ± 13.3 L/hr·kg ($p < 0.05$) (Table 1). Crucially, the absence of a statistically significant change in $T_{1/2}$, suggests that the primary mechanism is the induction of CYP1A2, the principal enzyme of melatonin metabolism, mainly affecting first-pass metabolism. Although this marked reduction in bioavailability is largely attributable to increased first-pass metabolism, the indirect effect of omeprazole on gastric physiology must also be considered. As a potent proton pump inhibitor, omeprazole elevates gastric pH [33]. Alterations in gastric pH could potentially modify drug absorption, thereby influencing its absorption kinetics. However, melatonin has two reported pKa values, a strong acidic pKa around 16.51 and a basic pka of -0.69 and because of these pKa values, melatonin remains neutral over a wide range of pH [34.] Thus, the substantial increase observed in clearance (Cl/F) strongly suggests that the reduction in systemic melatonin exposure is predominantly driven by CYP1A2 induction. This finding aligns with observations in smokers, a well-known CYP1A2 inducer, where the metabolic clearance of melatonin was observed to be 1.8-fold higher [35].

5. CONCLUSIONS

In summary, our findings illustrate that CYP1A2 induction by omeprazole significantly reduces the systemic exposure of melatonin in healthy Thai male volunteers. The marked interindividual variability observed further underscores the importance of considering genetic and environmental factors when evaluating melatonin pharmacokinetics. These data enhance our understanding of melatonin metabolism and highlight the need for further exploration of drug–drug interactions involving CYP1A2 substrates [35].

6. ACKNOWLEDGEMENTS

Author contribution

WT and NJ: Conception and study design; NJ, NN, SK, and WT: Subject enrollment; NJ, NN, and TK: Conducted the experiments; WT, NJ and SK: Performed data analysis; WT and NJ: Drafted the manuscript. All authors critically reviewed and approved the final manuscript.

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Conflict of interest

None to declare

Ethics approval

The study protocol was approved by the Khon Kaen University Ethics Committee for Human Research (approval number: HE561318).

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