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REVIEW ARTICLE

Clinical pharmacokinetics of melatonin: a systematic review

Nathja Groth Harpsøe[1] · **Lars Peter Holst Andersen**[1] · **Ismail Gögenur**[2] · **Jacob Rosenberg**[1]

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Abstract
Purpose The aim of the review was to provide an overview of studies investigating the pharmacokinetics of exogenous melatonin in humans and if possible, to provide recommendations for clinical use.
Methods The review was conducted in accordance to PRISMA guidelines. A systematic literature search was performed in PubMed and Embase databases. The pharmacokinetic variables included maximal plasma/serum concentration (C_{max}), time to maximal plasma/serum concentration (T_{max}), elimination half-life ($T_{1/2}$), area-under-the-curve plasma/serum concentrations (AUC), clearance (Cl), volume of distribution (V_D), and bioavailability.
Results The literature search identified 392 records. Twenty-two studies were included in the review. Melatonin dosages varied between 0.3 and 100 mg and were administered either orally or intravenously. C_{max} ranged from 72.1 (10 ml/h; 0.02 mg, IV) to 101,163 pg/ml (100 mg, oral). T_{max} ranged between 15 (2 mg) and 210 min (10 mg). $T_{1/2}$ ranged from 28 (0.005 mg, IV) to 126 min (4 mg, oral), whereas AUC ranged between 5400 (0.005 mg, IV) and 6.56×10^{10} pg/ml×min (1 mg, oral). Cl ranged from 0.97 (0.005 mg, IV) to 132.50 L/min (6 mg, oral), whereas V_D ranged between 35 (0.005 mg, IV) and 1602 L (4 mg, oral). Bioavailability of oral melatonin ranged from 9 to 33 %. Pharmacokinetics was affected by age, caffeine, smoking, oral contraceptives, feeding status, and fluvoxamine. Critically ill patients displayed accelerated absorption and compromised elimination.
Conclusions Despite methodological differences between the included studies, T_{max} was approximately 50 min following oral immediate-release formulations of melatonin. $T_{1/2}$ was 45 min in both administration routes. C_{max}, AUC, Cl, and V_D varied extensively between studies. Bioavailability of oral melatonin was approximately 15 %.

Keywords Exogenous · Melatonin · Patients · Pharmacokinetic · Volunteers

Introduction

The pineal hormone, melatonin regulates a variety of physiological functions, such as circadian rhythm, reproduction, mood, and immune function [1]. Correspondingly, exogenous melatonin has demonstrated a number of clinical effects [1, 2]. Numerous clinical studies have documented improved sleep quality following administration of exogenous melatonin [1, 3, 4]. Recent studies also demonstrate analgesic [4, 5], anxiolytic [5], anti-inflammatory [6], and anti-oxidative effects [6, 7] of melatonin.

In clinical studies, melatonin is typically administered orally, sublingually, or intravenously. Until now, the pharmacokinetics of melatonin has primarily been investigated in healthy volunteers following oral and intravenous administration of melatonin, but findings have been inconsistent [8, 9]. The increasing clinical use, however, necessitates further investigation of the pharmacokinetics of melatonin, and an overview of the current literature is urgently needed.

The aim of this systematic review was to provide a comprehensive overview of studies investigating pharmacokinetics of

✉ Nathja Groth Harpsøe
ng.harpsoee@gmail.com

[1] Department of Surgery D, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark

[2] Department of Surgery, Køge and Roskilde Hospital, University of Copenhagen, DK-4600 Køge, Denmark

exogenous melatonin in humans and if possible, to provide evidence-based recommendations for clinical use.

Methods

The review was performed in accordance to PRISMA guidelines [10] and registered at PROSPERO (CRD42014015040). A systematic literature search was conducted in PubMed and Embase databases in October 2014. The search strategy included following search algorithm: Melatonin AND (exogenous OR exogenously OR administration) AND (pharmacokinetic OR pharmacokinetics OR bioavailability). Furthermore, a manual snowball search was performed in the reference lists of the included studies. Two independent authors (NGH, LPHA) performed the literature search. If any disagreements occurred between the authors, consensus was achieved between all authors of the review.

The review included all studies written in English investigating pre-defined pharmacokinetic variables following exogenous administration of melatonin in adult volunteers and patients. Studies, which did not fulfill these criteria or investigated melatonin receptor agonists, were excluded from the review.

The pre-defined pharmacokinetic variables included the following: maximal plasma/serum concentration (C_{max}), time to maximal plasma/serum concentration (T_{max}), elimination half-life ($T_{1/2}$), area-under-the-curve plasma/serum concentrations (AUC), clearance (Cl), volume of distribution (V_D), and bioavailability (units: pg/ml, min, min, pg/ml×min, L/min, L, and %, respectively). If the pharmacokinetic variables appeared in different units than described above, relevant adjustments were performed. Body weight (BW)-adjustments of data were employed, if needed, applying a correction value of 75 kg BW. For oral administrations of melatonin, bioavailability-corrected values of Cl and V_D were employed and reported as Cl/F and V_D/F. Additional outcomes reported in the included studies, apart from the pre-defined pharmacokinetic variables, are not presented or evaluated in this review.

Results

The complete literature search is described in detail in Fig. 1. Twenty-two studies (n=359) were included in the review [3, 8, 9, 11–29].

Table 1 describes number of volunteers/patients, study design, volunteer/patient characteristics, measuring period, and reported pharmacokinetic variables.

The review included five randomized clinical trials (RCT) [3, 8, 17, 21, 28], 16 cohort studies [9, 11–16, 18–20, 22, 23, 25–27, 29], and one case report [24]. Nineteen studies included healthy volunteers [8, 9, 11–15, 17–20, 22–29]. Three clinical studies included critically ill patients [3, 16] and elderly patients suffering from insomnia [21], respectively.

Four studies administered melatonin by intravenous bolus injection [8, 12, 18, 24] in doses ranging from 0.0005 mg/kg to 2 mg [8, 12]. Two studies applied intravenous infusions in doses of 0.02 mg (10 ml/h) and 0.023 mg (250 ml/h) [18, 20], respectively. Eighteen studies administered oral melatonin (capsules: n=8 [11, 13, 15, 19, 25–28]/tablets: n=7 [16, 17, 21–23, 25, 29]/oral solutions: n=3 [3, 20, 25]/powders: n=1 [27]) in doses ranging from 0.3 [11] to 100 mg [13]. The studies investigating oral melatonin administered immediate-release formulations in 17 studies [3, 8, 9, 11, 13–17, 19, 20, 22, 23, 25, 27–29], surge-sustained release (25 % immediate-release+75 % controlled release) formulations in one study [21], pulsatile-release (immediate-release+secondary release) formulations in one study [28], and slow-release formulations in two studies [25, 26]. All oral administrations were single doses, except for one study administering three separate doses [15]. The measuring periods ranged from 2 to 36 h [15, 18]. Plasma/serum melatonin concentrations were assessed by radioimmunoassay (RIA) in 15 studies [3, 8, 11–13, 15–19, 21, 24, 25, 28, 29], by high-performance liquid chromatography (HPLC) in three studies [22, 23, 26] and by gas chromatography-mass spectrometry (GC-MS) in three studies [14, 20, 27]. One study did not report the applied assay technique [9].

Pharmacokinetic variables

The reported pharmacokinetic variables C_{max}, T_{max}, $T_{1/2}$, AUC, Cl, V_D, and bioavailability of each study are presented in Table 2.

C_{max} was measured in 18 studies [3, 8, 11, 13, 14, 16–23, 25–29]. C_{max} after intravenous bolus administration was 96,850 pg/ml (dose 2 mg) [8]. For intravenous infusions, C_{max} ranged between 72.1 pg/ml (dose 0.02 mg, 10 ml/h) [18] and 169.0 pg/ml (dose 0.023 mg, 250 ml/h) [20]. After oral administrations, C_{max} ranged from 170 (dose 0.3 mg) [11] to 101,163 pg/ml (dose 100 mg) [13].

T_{max} was reported in 17 studies [3, 11, 13–17, 19–28]. For intravenous infusions, T_{max} was 113.4 min for male volunteers and 110.4 min for female volunteers (dose 0.023 mg, 250 ml/h), respectively [20]. T_{max} for oral immediate-release formulations ranged from 15 (dose: 2 mg) [25] to 90 min (dose 25 mg) [19]. The oral surge-sustained formulations displayed T_{max} values of 78 and 90 min, respectively (dose 0.4 and 4 mg) [21]. Two different oral pulsatile-release formulations displayed T_{max} of 45 and 210 min, respectively (dose 10 mg) [28]. One study employing an oral slow-release formulation reported a T_{max} value of 167 min (dose 5 mg) [26].

$T_{1/2}$ was assessed in 18 studies [3, 8, 9, 12, 13, 15–18, 20–26, 28, 29]. After intravenous bolus administrations, $T_{1/2}$ ranged from 28 (dose 0.005 mg) [18] to 60 min (dose 2 mg)

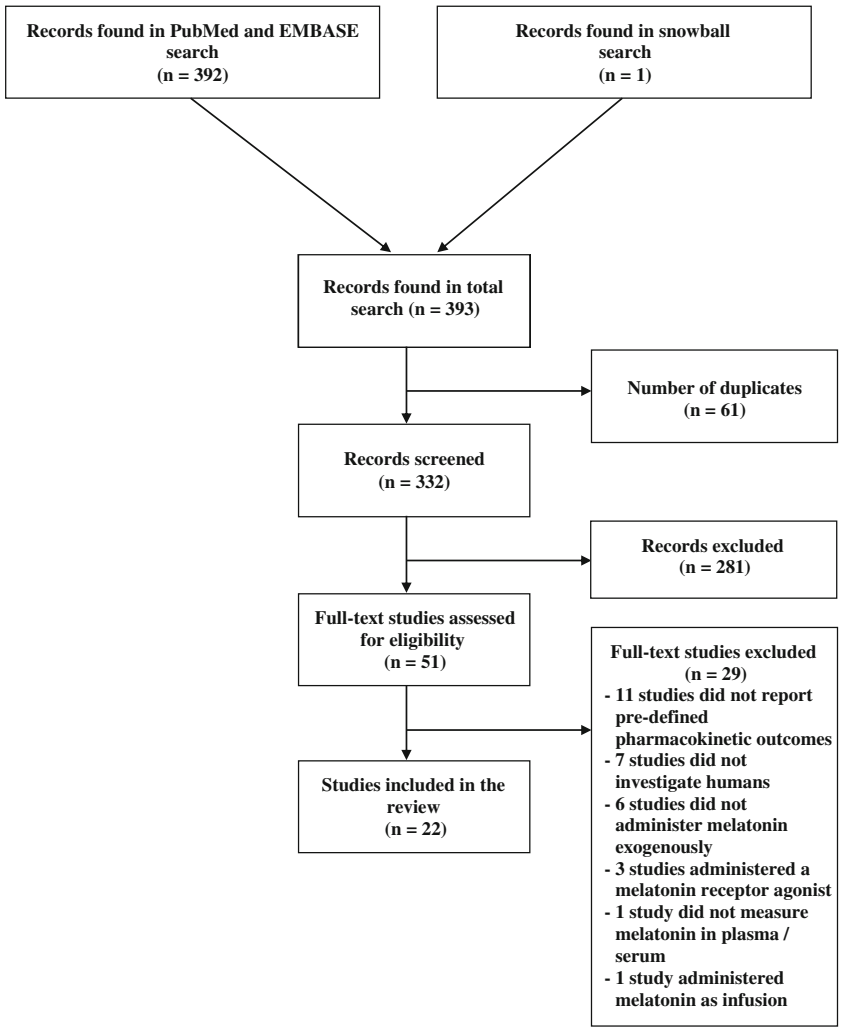

Fig. 1 PRISMA flowchart

[8]. After intravenous infusions, $T_{1/2}$ ranged between 36 (dose 0.023 mg, 250 ml/h) [20] and 45 min (dose 0.02 mg, 10 ml/h) [18]. Following oral administrations, $T_{1/2}$ ranged from 32 (dose 2 mg) [25] to 126 min (dose 4 mg) [21].

AUC was reported in 17 studies [3, 8, 11, 12, 15, 16, 18–23, 25–29]. AUC after intravenous bolus administrations ranged from 5400 pg/ml×min (dose 0.005 mg) [18] to 1.63×10^6 pg/ml×min (dose 2 mg) [8]. AUC for intravenous infusions was 15,288 pg/ml×min for male volunteers and 21,846 pg/ml×min for female volunteers (dose 0.023 mg, 250 ml/h), respectively [20]. Following oral administrations, AUC ranged between 6.56×10^{10} pg/ml×min (dose 1 mg) [27] and 14,160 pg/ml×min (dose 0.25 mg) [20]. One study, applying a multiple dosage regimen documented an AUC of 31.3×10^6 (dose 80 mg×3 per hour) [15].

Cl was reported in nine studies [3, 12, 17, 18, 20–23, 26]. Cl after intravenous bolus administrations ranged from 0.97 (dose 0.005 mg) [18] to 3.30 L/min (dose: 0.0005 mg/kg) [12]. After intravenous infusions, Cl ranged between 0.97 (dose 0.02 mg, 10 ml/h) [18] and 1.57 L/min (dose 0.023 mg, 250 ml/h) [20]. Following oral administrations, Cl/F ranged from 1.63 (dose 6 mg) [17] to 132.50 L/min (dose 6 mg) [23].

V_D was reported in five studies [12, 18, 20, 21, 26]. Following intravenous bolus administration, V_D ranged from 35 (dose 0.005 mg) [18] to 185 L (dose 0.0005 mg/kg) [12]. After intravenous infusions, V_D values ranged between 53.8 and 73.1 L (dose 0.023 mg, 250 ml/h) [20]. Following oral administrations, V_D/F ranged from 451 (dose 5 mg) [26] to 1602 L (dose 4 mg) [21].

Three studies reported absolute bioavailability [8, 9, 20]. Bioavailability ranged from 9 (dose 0.25 mg) [20] to 33 % (dose 0.5 mg) [9].

Internal factors

A cohort study including 36 volunteers investigated the effect of age [11]. Volunteers were grouped as either young (20–43 years) or older (49–73 years) subjects. The study did not document any significant differences in C_{max}, AUC or T_{max} values between the groups [11].

Table 1 Baseline characteristics of the included studies

Authors	Number of included volunteers/patients	Study design	Volunteer/patient characteristics	Measuring period	Pharmacokinetic variables
Aldhous et al. [25]	12	Cohort study	Healthy volunteers	7 h	C_{max} T_{max} $T_{1/2}$ AUC
Bourne et al. [3]	24	RCT	Critically ill patients	24 h	C_{max} T_{max} $T_{1/2}$ AUC Cl/F
Cavallo et al. [12]	33	Cohort study	Healthy volunteers	6 h	$T_{1/2}$ AUC Cl V_D
DeMuro et al. [8]	12	RCT	Healthy volunteers	8 h	C_{max} T_{max} $T_{1/2}$ AUC Bio
Di et al. [9]	4	Cohort study	Healthy volunteers	–	$T_{1/2}$ Bio
Fourtillan et al. [20]	12	Cohort study	Healthy volunteers	13 h	C_{max} T_{max} $T_{1/2}$ AUC Cl; Cl/F V_D; V_D/F Bio
Goonerathe et al. [21]	27	RCT	Elderly patients with insomnia	24 h	C_{max} T_{max} $T_{1/2}$ AUC Cl/F V_D/F
Härtter et al. [17]	12	RCT	Healthy volunteers	6 h	C_{max} T_{max} $T_{1/2}$ Cl/F
Härrter et al. [29]	5	Cohort study	Healthy volunteers	28 h	C_{max} $T_{1/2}$ AUC
Hilli et al. [23]	29	Cohort study	Healthy volunteers	7 h	C_{max} T_{max} $T_{1/2}$ AUC Cl/F
Hoffmann et al. [28]	15	RCT	Healthy volunteers	10.5 h	C_{max} T_{max} $T_{1/2}$ AUC
Le Bars et al. [24]	1	Case report	Healthy volunteer	–	T_{max} $T_{1/2}$
López-Gamboa et al. [26]	12	Cohort study	Healthy volunteers	24 h	C_{max} T_{max} $T_{1/2}$ AUC Cl/F V_D/F

Table 1 (continued)

Authors	Number of included volunteers/patients	Study design	Volunteer/patient characteristics	Measuring period	Pharmacokinetic variables
Mallo et al. [18]	7	Cohort study	Healthy volunteers	2 h	C_{max} $T_{1/2}$ AUC Cl V_D
Markantonis et al. [22]	18	Cohort study	Healthy volunteers	5 h	C_{max} T_{max} $T_{1/2}$ AUC Cl/F
Mistraletti et al. [16]	12	Cohort study	Critically ill patients	24 h	C_{max} T_{max} $T_{1/2}$ AUC
Proietti et al. [27]	60	Cohort study	Healthy volunteers	6 h	C_{max} T_{max} AUC
Shirakawa et al. [14]	7	Cohort study	Healthy volunteers	4 h	C_{max} T_{max}
Ursing et el. [19]	8	Cohort study	Healthy volunteers	6 h	C_{max} T_{max} AUC
Vakkuri et al. [13]	5	Cohort study	Healthy volunteers	6 h	C_{max} T_{max} $T_{1/2}$
Waldhauser et al. [15]	8	Cohort study	Healthy volunteers	36 h	$T_{1/2}$ AUC
Zhadanova et al. [11]	36	Cohort study	Healthy volunteers	9 h	C_{max} T_{max} AUC

Baseline characteristics and reported pre-defined pharmacokinetic variables of the included studies. The symbol (−) refers to studies not reporting data. *RCT* randomized clinical trial, *h* hours, C_{max} maximal plasma/serum concentration, T_{max} time to maximal plasma/serum concentration, $T_{1/2}$ elimination half-life, *Cl* clearance, V_D volume of distribution, *Cl/F* clearance (oral), V_D/F volume of distribution (oral), *Bio* bioavailability

The effect of age and gender was also investigated in another cohort study including 33 volunteers (6–31 years) [12]. Prepubertal volunteers (mean age=8.4 years) displayed significantly shorter $T_{1/2}$ and a lower AUC compared to adult volunteers (mean age=27.2 years). No difference between the genders was observed.

The effect of menopause was investigated in a cohort study including 18 female volunteers [22]. The pharmacokinetic variables C_{max}, T_{max}, $T_{1/2}$, AUC, and Cl/F of melatonin were not significantly different between premenopausal and postmenopausal women [22].

External factors

The effect of caffeine, cigarette smoking, and genotype on pharmacokinetic variables of melatonin was investigated in a RCT including 12 volunteers [17]. The volunteers were randomized to either melatonin (6 mg) or melatonin (6 mg) + caffeine (3×200 mg). Concomitant administration of caffeine increased C_{max} from 4480 to 10,618 pg/ml, increased $T_{1/2}$ from 106 to 113 min, and reduced Cl/F from 3.08 to 1.63 L/min compared to melatonin alone [17]. Furthermore, the study documented that cigarette smoking reduced C_{max} and increased $T_{1/2}$ values [17]. Specific genotypes of cytochrome P450 (CYP) enzymes also altered pharmacokinetics [17].

The effect of cigarette smoking was also investigated in a cohort study including eight habitual smokers [19]. The volunteers received 25 mg of oral melatonin daily during periods of smoking and smoking-free periods, respectively. Cigarette smoking reduced C_{max} from 1858 pg/ml (smoking-free period) compared to 640 pg/ml (smoking period). Also, AUC was reduced from 294,002 pg/ml×min during smoking-free periods to 102,419 pg/ml×min during periods of smoking. T_{max} values were identical between the groups [19].

Table 2 Pharmacokinetic variables of the included studies

Author	Melatonin dose/administration route/subgroup	C_{max} pg/ml	T_{max} min	$T_{1/2}$ min	AUC pg/ml×min	Cl; Cl/F L/min	V_D; V_D/F L	Bio %
Aldhous et al. [25]	2 mg/oral/gelatin-coated capsules	Fasting, 2800	Fasting, 15	32	222,720	–	–	–
		Fed, 6800	Fed, 30	–	482,160	–	–	–
	2 mg/oral/slow-release pills	–	–	–	–	–	–	–
	2 mg/oral/corn-oil preparation	Fasting, 3500	Fasting, 30	–	237,180	–	–	–
		Fed, 4400	Fed, 30	40	349,560	–	–	–
Bourne et al. [3]	10 mg/oral	14,974	30	88	1.80×10^6	5.85	–	–
Cavallo et al. [12]	0.0005 mg/kg BW/IV/prepubertal	–	–	40	15,054	3.30	185	–
	0.0005 mg/kg BW/IV/pubertal	–	–	47	18,006	2.70	173	–
	0.0005 mg/kg BW/IV/adults	–	–	47	22,614	2.03	135	–
DeMuro et al. [8]	2 mg/oral	2175	52	61	237.77×10^3	–	–	14
	4 mg/oral	5766	60	65	530.57×10^3	–	–	16
	2 mg/IV	96,850	–	60	1.63×10^6	–	–	–
Di et al. [9]	0.5 mg/oral	–	–	47	–	–	–	33[a]
Fourtillan et al. [20]	0.25 mg/oral/male	244	23	36	14,160	–	–	9
	0.25 mg/oral/female	624	23	45	42,084	–	–	17
	0.023 mg (250 ml/h)/IV infusion/male	124.8	113.4	36	15,288	1.57	73.1	–
	0.023 mg (250 ml/h)/IV infusion/female	169.0	110.4	41	21,846	1.09	53.8	–
Goonerathe et al. [21]	0.4 mg/oral	405	78	108	95,700	6.32	1035	–
	4 mg/oral	3999	90	126	727.4×10^3	7.97	1602	–
Härtter et al. [17]	6 mg/oral/+caffeine (smoker+non-smoker)	10,618	30	113	–	1.63	–	–
	6 mg/oral/−caffeine (smoker+non-smoker)	4480	60	106	–	3.08	–	–
Härrter et al. [29]	5 mg/oral/+fluvoxamine	25,100	–	804[b]	8.48×10^6	–	–	–
	5 mg/oral/−fluvaxamine	2180	–	564[b]	372×10^3	–	–	–
Hilli et al. [23]	6 mg/oral/wild-type genotype+OC	7900	60	36	684×10^3	12.50	–	–
	6 mg/oral/wild-type genotype−OC	1800	60	37	138×10^3	132.50	–	–
	6 mg/oral/variant genotype+OC	7200	60	38	654×10^3	15.63	–	–
	6 mg/oral/variant genotype−OC	1700	45	49	144×10^3	94.00	–	–
Hoffmann et al. [28]	5 mg/oral/immediate-release formulation (type A)	A=4823	A=30	A=38	A=256,885	–	–	–
	10 mg/oral/pulsatile-controlled release formulation (type B/C)	B=3820	B=45	B=48	B=507,911	–	–	–
		C=4072	C=210	C=50	C=595,400	–	–	–
Le Bars et al. [24]	Dose not reported/IV	–	4	44	–	–	–	–
López-Gamboa et al. [26]	5 mg/oral/slow-release	8770	167	91	2.3×10^6	3.09	451	–
Mallo et al. [18]	0.005 mg/IV bolus	–	–	28	5400	0.97	35	–
	0.02 mg (10 ml/h)/IV infusion	72.1	–	45	–	0.97	63	–
Markantonis et al. [22]	6 mg/oral/premenopausal women	16,756	30	46	1.18×10^6	8.44	–	–
	6 mg/oral/postmenopausal women	16,438	53	52	1.24×10^6	9.88	–	–
Mistraletti et al. [16]	3 mg/oral	11,040	16	94	1.69×10^6	–	–	–
Proietti et al. [27]	1 mg/oral/powder	799	60	–	2.11×10^{10}	–	–	–
	1 mg/oral/soft gel capsule	2620	60	–	6.56×10^{10}	–	–	–
	3 mg/oral/powder	2405	40	–	62.5×10^8	–	–	–
Shirakawa et al. [14]	3 mg/oral	3561	20	–	–	–	–	–
Ursing et el. [19]	25 mg/oral/+smoking	640	90	–	102,419	–	–	–
	25 mg/oral/−smoking	1858	90		294,002			
Vakkuri et al. [13]	100 mg/oral	101,163	60	41	–	–	–	–
Waldhauser et al. [15]	80 mg/oral	–	–	48	27.87×10^6	–	–	–
	80 mg×3/oral	–	–	–	31.3×10^6	–	–	–
Zhadanova et al. [11]	0.3 mg/oral/age, 20–43 yrs	170	48	–	26,514	–	–	–
	0.3 mg/oral/age, 49–73 yrs	255	45	–	35,748	–	–	–

The symbol (−) refers to studies not reporting the pre-defined pharmacokinetic variable, or not reporting a mean/median-data value of the specific variable. Dosages relate to the reported pharmacokinetic variables, not additional dosages administered in the same study.

C_{max} maximal plasma/serum concentration, T_{max} time to maximal plasma/serum concentration, $T_{1/2}$ elimination half-life, *Cl* clearance, V_D volume of distribution, *bio* bioavailability, *yrs* years, *BW* body weight, *IV* intravenous, *OC* oral contraceptives

[a] Bioavailability was reported in the study. No other pharmacokinetic data for intravenous administration was reported.

[b] The reported values for $T_{1/2}$ must be due to an error, and is omitted from the manuscript.

The effect of oral contraceptives (OC) and genotype of CYP-enzymes was investigated in a cohort study including 29 volunteers [23]. Following oral administration of 6 mg of melatonin, OC significantly increased C_{max} and AUC and reduced Cl/F values [23]. Furthermore, the genotype of CYP-enzymes (wild-type allele or variant allele) was assessed. Genotypes did not affect the pharmacokinetics of melatonin [23].

A cohort study including 12 volunteers administered 2 mg of oral melatonin in different oral formulations in fed and fasting state, respectively [25]. C_{max} and AUC were increased during fed state; however, statistical comparisons were not performed. The study documented similar T_{max} values between the groups. $T_{1/2}$ ranged from 32 (gelatin-coated capsules, fasting state) to 40 min (corn-oil preparation, fed state).

The effect of co-administration of 50 mg of fluvoxamine and 5 mg of melatonin was investigated in a cohort study including five male volunteers [29]. C_{max}, AUC, and $T_{1/2}$ values were significantly increased with the co-administration of fluvoxamine.

Pharmacokinetics in patients

The pharmacokinetics of melatonin has been investigated in three studies investigating critically ill patients [3, 16] and elderly patients with insomnia [21], respectively.

A RCT investigating 24 critically ill patients administered either 10 mg of oral melatonin or placebo [3]. The melatonin group exhibited a C_{max} of 14,974 pg/ml, a T_{max} of 30 min, a $T_{1/2}$ of 88 min, and an AUC of 1.80×10^6 pg/ml×min.

Mistraletti and colleagues investigated a cohort of 12 critically ill patients [16]. An oral dose of 3 mg melatonin was administered as crushed tablets by a nasogastric tube. The study demonstrated a C_{max} of 11,040 pg/ml, a T_{max} of 16 min, a $T_{1/2}$ of 94 min, and an AUC of 1.69×10^6 pg/ml× min.

A two-arm RCT investigated 27 elderly patients suffering from insomnia [21]. The study administered two surge-sustained release formulations (dose 0.4/4 mg), respectively. C_{max} and AUC were significantly higher in the high-dose group compared to the low-dose group. No differences in T_{max}, $T_{1/2}$, Cl/F, or V_D/F values were demonstrated between the groups.

Discussion

The pharmacokinetics of exogenous melatonin has primarily been investigated in healthy volunteers. The studies investigating oral immediate-release formulations demonstrated T_{max} values of approximately 50 min. A $T_{1/2}$ of approximately 45 min was documented following both oral and intravenous administrations. Studies administering oral slow-release formulations demonstrated prolonged T_{max} and $T_{1/2}$ values of up to 167 and 91 min, respectively.

Our review displayed extensive variations within- and between studies with respect to the pharmacokinetic variables, C_{max}, AUC, Cl, and V_D. These variations may obviously be caused by individual differences in absorption, distribution, metabolism, and elimination of the drug, though further details are not known at this moment [9, 20]. It should, however, be investigated, if these variations may potentially affect drug efficacy. Interestingly, no link between specific melatonin plasma concentration levels and actual clinical effects (or adverse effects) has been established yet. Furthermore, the low number of included studies and the differences in study designs, dosages (0.3–100 mg), administration routes (oral and IV), drug formulations, and melatonin analysis assays may also have contributed to the variability of data. Regarding the use of different analysis assays, it might be a significant factor to the observed variability of the results. Interestingly, no studies performing direct comparisons of the different assays have performed so far.

Our review also demonstrated a low bioavailability [8, 9]. It may either result from low absorption from the gastrointestinal canal, from an extensive first-pass metabolism in the liver or from a combination of both [9]. At this moment, the exact intestinal absorption fraction of oral melatonin in humans is not established [20]. On the other hand, Di and colleagues documented an increased metabolite production following oral administration compared to intravenous, indicating first-pass metabolism as the primary determinant [9]. Assessments of bioavailability may, however, also be affected by the administration of different drug formulations. It is crucial that the measuring periods should be adapted to the prolonged absorption phase of e.g., slow-release formulations in order not to underestimate the bioavailability of the drug (or at least estimate bioavailability by applying the elimination constant and last measured plasma/serum concentration). Future studies investigating bioavailability should attempt to provide detailed pharmacokinetic analyses of metabolites following melatonin administration by different administration routes. Moreover, further investigations of the physiological and possible clinical effects of melatonin metabolites, such as 6-sulfatoxymelatonin, N-acetyl-5-methoxykynuramine (AMK), and N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK) are needed [30]. Conclusively, studies also indicated a substantial intra-study variability of bioavailability, demonstrated by values ranging between 10 and 56 % [9]. This variability was, however, not present to the same extend in a recent high-quality study [8]. Future studies should examine, if inter-individual variations of bioavailability are actually present, or caused by methodological differences between the studies.

Our review also documented that external factors, such as caffeine [17], cigarette smoking [19], OC [23] and fluvoxamine [29] either increased [17, 23, 29] or reduced C_{max} and AUC values of melatonin. Correspondingly, elimination rates ($T_{1/2}$ and Cl) were reduced [23, 29] or increased [17]. In this case, the altered pharmacokinetics probably results from an altered metabolism by specific CYP-enzymes in the liver [17, 19, 29]. Especially, the CYP 1A2 enzyme seems to play a key role in the metabolism of melatonin. Other external factors, such as fasting also reduced C_{max} compared to fed state [25]. These findings may influence future dosing regimens in surgical patients receiving perioperative melatonin treatments [2, 25]. In critically ill patients, an accelerated T_{max} and extended $T_{1/2}$ were demonstrated, probably due to a reduced liver and kidney function in this patient category [3, 16]. In general, the effects of external factors may mandate alternative dosing regimens in selected patient groups. Otherwise, risks of inadequate drug plasma concentrations or clinical "hangover" effects due to increased/prolonged plasma concentrations may occur. It should, however, be underlined that studies in "standard" medical (without serious comorbidity) and surgical patients should be performed before differences in pharmacokinetics between volunteers and patients can be finally settled.

This review was performed in accordance to PRISMA guidelines [10]. It is the first systematic review to provide a comprehensive overview of the literature concerning the pharmacokinetics of melatonin in adult volunteers and patients. We chose not to include a quality or risk of bias analysis due to the heterogeneous nature of the included studies (RCTs, cohort and case reports studies in both volunteers and patient) [31, 32]. Furthermore, the pharmacokinetic variables assessed in this review do not relate to potential bias or quality parameters (e.g., randomization and blinding) evaluated by these scoring systems. Finally, no quantitative analysis was feasible, also due to the extensive variation in study designs, analysis methods, dosages, and administration routes.

In conclusion, this review documented a T_{max} of approximately 50 min following oral immediate-release formulations of melatonin. $T_{1/2}$ of both oral and intravenous melatonin was about 45 min. An administration of melatonin 45 min before intended clinical effect may therefore be advocated. A clinician should also consider external factors, which may potentially affect the pharmacokinetics of melatonin. C_{max}, AUC, Cl, and V_D displayed extensive variation within and between studies. The variations may obviously relate to inter-individual differences in drug absorption, distribution, metabolism, and elimination but may also be confounded by substantial variability in study designs/methods. Bioavailability was generally low (approximately 15 %) and potentially with a significant intra-individual variability.

Conflict of interest The authors declare that they have no competing interests.

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