Use of immediate release melatonin in psychiatry: BMI impacts the daily-dose

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[Utilisation de la mélatonine à libération immédiate en psychiatrie : L'IMC impacte le choix de la dose journalière]

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***Running head** : Melatonin use in psychiatry*

Abstract

Objective: There is a growing interest in psychiatry regarding melatonin use both for its soporific and chronobiotic effects. This study aimed to evaluate factors impacting the daily-dose. Methods: In a university department of psychiatry in Paris (France), we conducted a posteriori naturalistic observational study from April 03, 2017 to January 31, 2018. We assessed links between sociodemographic and clinical characteristics and daily dose of melatonin (the daily-dose of melatonin initiation and the daily-dose at Hospital discharge). A survey of drug interactions was performed regarding metabolic inducers and inhibitors of the cytochrome P450 1A2. Results: Forty patients were included and treated with immediate-release melatonin. For patients with no history of melatonin use, the initiation dose of was 2 or 4 mg, with no effects of age, weight, BMI, melatonin indication, cause of hospitalization. We found that higher discharge dose was associated with higher BMI (p=0.036) and more reevaluations of melatonin dose (p=0.00019). All patients with a moderate inducer (n=3, here lansoprazole) were significantly more associated with the discontinuation melatonin group (p=0.002). Conclusion: The BMI and the number of reevaluations impact the daily dose of melatonin. Two mechanisms may explain that BMI may need higher doses: i) melatonin diffuses into the fat mass, ii) the variant 24E on melatonin receptor MT2, more frequent in obese patients, leads to a decrease of the receptor signal.

Keywords: melatonin; insomnia; depression: bipolar disorders; sleep; circadian rhythms; cytochrome; metabolic inducer; metabolic inhibitor.

Resume

Objectif : La mélatonine bénéficie d'un intérêt clinique croissant et est de plus en plus utilisée dans les troubles psychiatriques, tant pour ses effets soporifiques que pour ses effets chronobiotiques. Cette étude a pour objectif d'évaluer les facteurs pouvant avoir un impact sur la dose quotidienne de mélatonine utilisée en psychiatrie. Méthodologie : Dans un département universitaire de psychiatrie à Paris (France), nous avons mené une étude observationnelle pragmatique à posteriori du 03 avril 2017 au 31 janvier 2018. Nous avons évalué les liens entre les caractéristiques sociodémographiques et cliniques et la dose journalière de mélatonine (dose d'initiation et dose de sortie d'hospitalisation). De plus, une étude des interactions médicamenteuses a été réalisée concernant les inducteurs métaboliques et les inhibiteurs du cytochrome P450 1A2. Résultats : Quarante patients ont été inclus et traités avec de la mélatonine à libération immédiate. Pour les patients sans antécédent d'utilisation de mélatonine, les doses d'initiation étaient soit 2 ou 4 mg. L'âge, le poids, l'Indice de Masse Corporelle (IMC), l'indication de la mélatonine et la cause de l'hospitalisation n'avaient aucune influence retrouvée sur la dose d'initiation de mélatonine. Au cours de l'hospitalisation, la période médiane entre chaque réévaluation de dose de mélatonine était de 4,5 jours. En sortie d'hospitalisation, la dose médiane de mélatonine était de 4mg. Nous avons constaté que l'utilisation de doses élevées de mélatonine était associée à un IMC plus élevé (p=0,036) et un nombre de réévaluations des doses de mélatonine au cours de l'hospitalisation plus élevé (p=0,00019). Tous les patients ayant un inducteur modéré (n=3, ici le lansoprazole) ont été significativement plus associés au groupe ayant cessé de prendre de la mélatonine (p=0,002).

Conclusion : L'IMC et le nombre de réévaluations semblent avoir un impact sur la dose quotidienne de mélatonine. Deux mécanismes peuvent être évoqués pour expliquer l'utilisation de dose plus élevée chez les personnes avec un IMC plus élevée : i) la mélatonine se diffuse dans la masse graisseuse, ii) le variant 24E du récepteur de la mélatonine MT2, plus fréquente chez les patients obèses, entraîne une diminution du signal du récepteur.

Mots-clés : mélatonine ; insomnie ; dépression : troubles bipolaires ; sommeil ; rythmes circadiens ; cytochrome ; inducteur métabolique ; inhibiteur métabolique.

Introduction

There is a growing interest in psychiatry regarding the use of melatonin, a natural mammal hormone secreted in the brain by the pineal gland during the night (1). Its main physiological function is to synchronize circadian rhythms of both central and peripheral clocks (1). The melatonin structure is indole, neutral and lipophilic (2). Exogenous melatonin is used in clinical settings to treat patients with delayed sleep phase disorders (3), and to improve sleep parameters and overall sleep quality (4). Regarding psychiatric disorders, several studies suggested that melatonin may improve sleep and behavioural symptoms in children with autistic spectrum disorders (5–8), bipolar disorders (9,10), metabolic syndrome secondary to antipsychotics (11), and benzodiazepine discontinuation (12). Nevertheless, the dose of melatonin may differ between indications but also within disorders (13,14). Indeed, the melatonin daily dose reported goes from 0.125 to 12 mg (10–12,15–20), but most of these studies used daily doses between 2 and 6 mg of immediate-release melatonin (11,16,17).

In France, melatonin is considered as a psycholeptic drug from 2 mg per day, and as a dietary supplement under 2mg per day (14). Nowadays, only one pharmaceutical formulation of melatonin is available for physicians as extended-release tablets of 2 mg for treating primary insomnia in adults >55 year-old and children with neurodevelopmental disorders (14). The melatonin induces both circadian-related and sleep-related responses: i) a chronobiotic action synchronizing biological rhythms, and ii) a soporific effect increasing with the dose (14). Both effects may be of interest in psychiatric disorders (19,21–23). The chronobiotic effect appears stronger with the immediate-release formulation than the extended-release one, as demonstrated for instance in the seasonal affective

disorder (19,24). In this context of an absence of available pharmaceutical drugs in its immediate release formulation, we prepared immediate-release melatonin capsules of 2 and 5 mg for the psychiatry department. This study aimed to evaluate factors impacting the daily-dose of melatonin initiation and the daily-dose at discharge of hospitalization. We also aimed to evaluate effects of metabolic inducers and inhibitors of the cytochrome P450 1A2.

Methods

Population and settings

In a university department of psychiatry for adults in Paris, France (Fernand-Widal Hospital), psychiatrists could prescribe immediate-release melatonin for the following documented indications:

- delayed sleep phase disorder ;
- insomnia sleep disorders (sleep onset latencies and total sleep time and/or overall sleep quality);
- bipolar disorders ;
- metabolic syndrome secondary to antipsychotics ;
- benzodiazepine discontinuation.

Immediate-release melatonin capsules were manufactured and dispensed by the pharmacy department. We use here data drawn from patients who benefited from melatonin between April 03, 2017 and January 31, 2018.

Ethics approval

This is a case series for which informed and written consents were obtained for all patients, with specific information regarding the off-label use of melatonin.

Assessments

A routine clinical monitoring of patients was performed by psychiatrists and pharmacists, and the following parameters were available for each patient in his medical file:

- sex ;
- age ;
- weight;
- height;
- body mass index (= weight /(height)²) ;
- cause of hospital admission ;
- melatonin indication ;
- history of extended-release melatonin use;
- initial daily dose ;
- time of melatonin prescription
- time of melatonin administration
- discharge daily dose or discontinuation daily dose ;
- cause of discontinuation ;
- duration of treatment follow-up;
- number of reevaluations of melatonin daily-dose. No instructions were proposed to psychiatrists regarding reevaluation recommendations;
- duration between two reevaluations.

A drug interactions survey was conducted both at initiation time and at the patient discharge or discontinuation time. Cytochrome P450 1A2 (CYP1A2) is the cytochrome predominantly involved in the systemic metabolism of melatonin (25,26). Therefore co-prescription of inducers or inhibitors of CYP1A2 were analyzed. Each inducer or inhibitor substance was categorized as powerful or moderate depending on its impact on the CYP1A2 activity (27) :

- **Strong inducers** of CYP1A2: tar (in tobacco composition) ;
- **Moderate inducers** of CYP1A2: carbamazepine, modafinil, lansoprazole, omeprazole ;
- **Strong inhibitors** of CYP1A2: norfloxacine, ciprofloxacine, fluvoxamine, dihydralazine ;

- **Moderate inhibitors** of CYP1A2: quetiapine, sertraline, cannabidiol, paroxetine, fluoxetine, ethinylestradiol, moclobemide, propafenone, tipranavir+ritonavir, verapamil, cannabis.

For non-drug substances survey, the active use of cannabis and tobacco was reported in the patient's medical file. For each patient the number of inducers or inhibitors was estimated.

Statistical analysis

Statistical analysis was performed with R® statistical software (version 3.3.0). The alpha risk chosen was 5%. Student and non-parametric Mann Whitney Wilcoxon, Pearson's Chi-squared, Kruskal-Wallis and Fisher's exact test were used. Correlation tests were performed with the Pearson's method for variables with normal distributions, and with the Spearman's method for non-normal distributions. Then, linear and logistic regressions were used to evaluate the influence between the significant characteristics, identified in univariate analyses, and the discharge dose of melatonin.

Results

Forty patients treated with immediate-release melatonin were included in our study: 25 women (62.5%) and 15 men (37.5%). Means (± standard deviation) for age, weight and BMI were 48.6 ± 13.3 years, 68.9 ± 13.5 kg, and 23.9 ± 4.4 $kg.m^{-2}$, respectively. Patients were hospitalized for bipolar disorder (n=19), major depressive episode (n=15) or substance withdrawal (n=6). Immediate-release melatonin was initiated in patients for insomnia sleep disorder (n=33, 82.5%), delayed sleep phase disorder (n=6, 15%), and benzodiazepine discontinuation (n=1, 2.5%). Clinical and demographics characteristics of the population are presented in Table 1.

Five patients (12.5%) were already treated with melatonin before hospitalization: two with extended-release and three with immediate-release melatonin. Patients treated with immediate-release melatonin benefited of daily dose of 5 and 6 mg before admission (two patients). Patients treated with extended-release melatonin all benefited from daily dose of 6 mg before admission. Overall, no adverse events were reported.

For melatonin-naive patients (n=35) the median (min-max) initiation dose was 2 mg (2-4). No impacts of age, weight and BMI, therapeutic indication or the cause of hospital admission was found on the initiation daily dose.

The melatonin treatment characteristics for the 40 patients are presented in Table 2. Only 12.5% of them benefited from at least three reevaluations of the melatonin dose during the period of treatment follow-up. The median period between each dose reevaluation was 4.5 days (2,0-21,0). No impacts of the indication or the cause of hospital admission was associated with the discharge rate or the discontinuation dose. No adverse events were reported.

The immediate-release melatonin was discontinued for six patients (all women) prior to discharge: one woman discontinued the melatonin treatment (8 mg then 4mg) since we observed an improvement of insomnia sleep disorders; whereas the five remaining women presented no improvement: one with 12 mg of melatonin, one with 10 mg of melatonin and three patients with 6 mg of melatonin (all patients have been switched to extended-release melatonin, including two patients treated with extended-release melatonin prior to hospitalization).

Median discontinuation dose was mg 7 mg (4-12). Melatonin was stopped after 22 days (6-51). Regarding time schedules, melatonin was prescribed at 10:00 PM (n=28), 9:00 PM (n=11) or 8:00 PM (n=1). The median difference between the time of prescription and administration was 21min (0-223). At the discharge of hospitalization for the 34 remaining patients, median dose was 4 mg (2-10). In addition, the discharge dose was 2 mg for 20.6% of patients (n=7). The median duration of treatment follow-up was 16 days (3-67). Regarding potential drug-drug interactions, no patients were treated with strong inhibitors of CYP1A2 during the study. Thirteen patients received a moderate inhibitor of CYP1A2 including one patient with two moderate inhibitors at the discharge. The moderate CYP1A2 inhibitors were: fluoxetine (n=11), paroxetine (n=9), quetiapine (n=5), sertraline (n=2), cannabis (n=13).

Concerning the metabolic inducers of CYP1A2, only tobacco produced a powerful inducing effect (n=14, including five patients who also had a moderate inhibitor). Three patients received a moderate inducer, which was lansoprazole for all of them. All patients receiving lansoprazole (including two tobacco smokers) were part of the discontinuation melatonin group (*vs* discharge melatonin, p=0.002).

No impact of gender was reported on the prescription of inducers and/or inhibitors of CYP1A2, nor the use of tobacco or cannabis. The discontinuation and discharge dosing regimens according to the co-administration or the concomitant use of CYP1A2 inhibitors or inducers are presented in Table 3.

A correlation matrix was performed between the quantitative variables (BMI, weight, age, discharge dosing, initial dosing, number of dose reevaluation, duration of treatment). The results are presented in Table 4. We observed significant correlations between BMI, discharge dosing, and number of dose reevaluation.

Based on the latter results, a multivariate logistic regression was performed to describe the melatonin discharge dose (DD). The two remaining explanatory factors were the BMI and the number of reevaluations, without interactions between both covariates. The regression residuals followed a normal distribution. The odds ratio table (Table 5) confirmed independent and significant effects on the DD of the number of reevaluations and the BMI, with ORs of 2.36 and 1.14 respectively.

Discussion

This preliminary report highlights a potential influence of BMI and the number of reevaluations on the discharge dose of melatonin prescribed during a hospitalization for psychiatric disorders. We also observed no influence of the indication or the cause of hospitalization associated with the initiation, discharge or discontinuation dose. Moreover, patients with a moderate inducer were significantly associated with the discontinuation melatonin group.

For most patients, the indication for melatonin use was insomnia. The initiation dose of melatonin was 2 or 4 mg. None of the assessed factors were associated with the decision to initiate between these two

doses. A dose of melatonin higher or equal to 2 mg leads to a dose-dependent soporific effect which may improve insomnia symptoms (19,28). Regarding the chronobiotic effect (e.g. synchronization of sleep-wake rhythms), Burgess *et al.* reported that melatonin effects on circadian rhythm were similar between 0.5 mg and 3 mg (29). Thus, since 20% of our patients received a putative efficient discharge dose of 2 mg, we propose an initiation of melatonin at the lowest dose with a titration depending on clinical efficacy.

Chronobiotic effects may need several days, and a treatment duration of three days appears sufficient to resynchronize circadian rhythms (29). These results are consistent with the median time to treatment reevaluation during hospitalization reported in our study (4.5 days).

This study confirmed in the multivariate analysis that higher a BMI is associated with an increased melatonin discharge dose. Links between body weight effects and melatonin secretion have been observed in previous works (30). Ferrier and colleagues reported that patients suffering from schizophrenia, compared to a control population, have significantly lower melatonin levels related to increased body weight (30). Contrasted results were observed in other studies in populations without psychiatric disorders, with some studies finding no links between obesity and urinary melatonin (31), others suggesting increased melatonin in the obese population (32–34), and finally others reporting a decrease in melatonin levels (33,35,36).

Beyond the potentially decreased endogenous melatonin levels, two other pharmacodynamic/pharmacokinetic effects may explain the use of increased melatonin in patients with a higher BMI.

First, an increase in body fat that generates an increase in drug diffusion. Doses must therefore be increased to obtain the same effective plasma concentration. In the review of Harpsøe et al., authors refer to the distribution volumes found in different pharmacokinetic studies (21). In a study using intravenous administration in an adult population, the mean distribution volume was 72L. It is commonly admitted that when a molecule exceeds 70 L of volume of distribution, this molecule has

an affinity for the fat mass. The latter physicochemical property probably allows the penetration of melatonin through a physiological barrier, such as the brain-blood barrier, and so in deep compartments. Thus for the same dose of melatonin, a patient with a higher BMI may have a lower plasma concentration.

Secondly, a common variant (24E) in the melatonin receptor type 1B (MT2) is more frequent in individuals with increased body weight (37). This variant 24E of MT2 is indeed associated with monogenic forms of hyperglycemia, type 2 diabetes, or related metabolic traits (37) and impacts the MT2 receptor signaling (37). It has been observed that a dose response still exists for this variant 24E, but the ligand-independent constitutive signaling is decreased (e.g. the signal mediated by the activation of the receptor is decreased independently of the dose) (37).

Regarding the metabolism of melatonin by CYP1A2, we observed that lansoprazole was significantly associated with the discontinuation melatonin group. Nevertheless, the unexpected absence of impact of tobacco in our study might be due to a lack of statistical power but also to a lack of precision in its daily consumption (number of cigarettes per day, for instance). When prescribing melatonin, it is recommended to take into account metabolic inducers or inhibitors and to explore the polymorphism of cytochrome CYP1A2 in case of adverse effects or ineffectiveness of the treatment (21,26).

Limitations of this study are related to its pragmatic nature. Indeed, the naturalistic design allowed to monitor routine clinical parameters, but no validated scales were used to follow symptoms such as depressive symptoms, circadian rhythms and insomnia symptoms. The pharmacy department was unable to manufacture capsules of 0.5 mg and 1 mg of melatonin due to the technical and analytical limits for the quality control assessments. We cannot guarantee that discharge doses were effective as no proper clinical scales were used. The treatment efficacy was monitored and subjectively reassessed by the physician.

Conclusion

This study observed that the BMI and the number of reevaluations impact the daily dose of melatonin prescribed for psychiatric disorders. Higher BMI may need higher doses. Two mechanisms may explain this finding: i) melatonin diffuses into the fat mass, ii) the variant 24E on melatonin receptor MT2, more frequent in obese patients, leads to a decrease of the receptor signal. Finally, attention should be made to metabolic inducers and inhibitors of cytochrome P450 1A2, which may impact the dose effect.

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Conflicts of Interest

Authors have no conflicts of interest related to this work.

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Table 1: Clinical and demographic characteristics of patients included in the study.

	Women (n= 25)	**Men (n=15)**	*p*
Age (year)	50.4 ± 13.7	45.6 ± 12.5	0.27
Weight (kg)	63.8 ± 11.8	77.2 ± 12.4	**0.002**
Body Mass Index ($kg.m^{-2}$)	24.0 ± 4.7	23.9 ± 3.9	0.71
Cause of Hospitalization – Bipolar disorder – Characterized depressive episode – Drug withdrawal	 16 6 3	 3 9 3	**0.024**
Melatonin indication – Insomnia sleep disorders – Delayed sleep phase disorder – Benzodiazepine discontinuation	 20 4 1	 13 2 0	0.32

In bold are indicated $p<0.05$

Table 2: Melatonin treatment characteristics

	All patients (n=40)
Melatonin discontinuation before discharge	6
Discharge daily dose (mg), median (min-max), **n=34**	4 (2-10)
Treatment duration (days), median (min-max), **n=34**	16 (3-67)
Number of dosing reevaluation during treatment • 0 • 1 • 2 • 3 • 4 • 5	 15 (37.5%) 16 (40%) 4 (10%) 2 (5%) 2 (5%) 1(2.5%)
Duration between two reevaluations (days), median (min-max)	4.5 (2.0-21.0)

Table 3: Discontinuation and discharge dosing regimens according to the co-administration or the concomitant use of CYP1A2 inhibitors or inducers

	Cannabis use (moderate CYP1A2 inhibitor)			Tobacco use (strong CYP1A2inducer)			Moderate CYP1A2 inducer			Moderate CYP1A2 inhibitor		
	Yes	No	p	Yes	No	p	Yes	No	p	Yes	No	p
Discharge Dose Median (mg) (min-max)	4 (2-6) (n=12)	4 (2-10) (n=22)	.63	4 (2-10) (n=11)	4 (2-8) (n=23)	.83	(n=0)	4 (2-10) (n=34)	NA	4 (2-8) (n=9)	4 (2-10) (n=24)	.59
Discontinuation Dose Median (mg) (min-max)	10 (n=1)	6 (4-12) (n=5)	.67	7 (4-10) (n=2)	7 (7-12) (n=4)	.80	5 (4-6) (n=3)	10 (8-12) (n=3)	.35	7 (5-12) (n=4)	7 (4-10) (n=2)	.80

Table 4: Correlation matrix between putative factors involved in the melatonin prescription

	Age	Weight	BMI	Initial daily dose	Discharge daily dose	Number of dose reevaluation	Duration of treatment follow-up
Age							
Weight	-0.1						
BMI	0.1	**0.7***					
Initial daily dose	-0.2	0.3	0.1				
Discharge daily dose	0.0	0.3	**0.5***	0.3			
Number of dose reevaluation	0.2	0.0	**0.3***	-0.1	**0.7***		
Duration of treatment	0.2	0.1	0.1	0.0	**0.4***	**0.6***	

*In bold are indicated $p<0.05$

Table 5: Multivariate linear regression examining the melatonin dose discharge depending on the number of reevaluation and body mass index.

	Estimate	Standard Error	T value	OR (IC 95%)	p
Intercept	0.59	1.35	0.44	1.80 (0.13-25.06)	0.67
Number of reevaluation	0.86	0.20	4.25	2.36 (1.59_3.51)	**0.00019**
Body Mass Index	0.13	0.06	2.20	1.14 (1.01-1.27)	**0.036**