

Recovery of circadian melatonin rhythm after a melatonin holiday in daytime haemodialysis patients on long-term exogenous melatonin

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Summary

The effects of exogenous melatonin on sleep diminish after its long-term use in haemodialysis patients. Our aim was to determine whether melatonin levels accumulate after chronic (at least three months) use of exogenous melatonin, 5 mg daily, and whether discontinuation of this treatment improves endogenous melatonin production and improves the circadian sleep-wake rhythm.

In this case series, stable haemodialysis patients discontinued their chronic exogenous melatonin usage for seven days and melatonin concentrations in saliva were analysed.

The primary endpoint was recovery of a normal circadian melatonin rhythm. Secondary endpoints were the effects on melatonin pharmacokinetics and sleep parameters.

At day three after discontinuation the normal circadian melatonin rhythm recovered in the two patients who discontinued the treatment for the full week. They also had an effective maximum trough level of melatonin.

Discontinuing melatonin seems to result in recovery of the circadian rhythm, based on achievement of effective melatonin thresholds.

Further research is necessary to investigate whether sleep parameters improve after a drug holiday. most appropriate treatment.

KEY WORDS: circadian rhythm, drug holiday, haemodialysis, melatonin, stop-week.

Introduction

Melatonin plays an important role in the human circadian sleep-wake rhythm (Nagtegaal et al., 2001). In healthy people, synthesis of endogenous melatonin starts to increase at twilight (Nagtegaal et al., 2001), a phenomenon termed dim light melatonin onset (DLMO) (Czeisler et al. 2005). DLMO results in drowsiness and facilitates sleep onset (Czeisler et al., 2005; Koch et al., 2008).

Sleep problems are frequently seen in patients on haemodialysis (Parker, 2003), and an impaired melatonin rhythm is often observed in patients with renal impairment, associated with sleep onset difficulties. In haemodialysis patients, both the DLMO and melatonin peaks are completely absent (Koch et al., 2010; Russcher et al., 2012). Administration of exogenous melatonin in the evening was found to partly restore the melatonin rhythm in haemodialysis patients (Koch et al., 2010; Russcher et al., 2012). After six weeks of treatment, improvements were recorded in clinical, sleep-related parameters (Koch et al., 2009). Unfortunately, long-term effects of exogenous melatonin were not confirmed. In the Melody study, in which high melatonin levels were found in saliva samples from haemodialysis patients after six months of exogenous melatonin use, sleep parameters worsened after 6-12 months (Russcher et al., 2013).

One hypothesis regarding the reduced effectiveness of exogenous melatonin after six months, which would also explain the finding of high daytime levels of the hormone, is that melatonin accumulates over time, causing the difference between its daytime and night time levels to diminish. Indeed, in the presence of high daytime melatonin levels, the melatonin trough threshold for effective DLMO (Koch et al., 2012) cannot be reached. This threshold corresponds, in saliva, to a maximum of 4 pg/ml (Nagtegaal et al., 1998).

Data on melatonin concentrations in patients on haemodialysis and undergoing prolonged melatonin treatment are lacking. The aim of this study was therefore to determine whether melatonin accumulates after administration of daily 5 mg dosages for a period of at least three months, and whether discontinuation of the treatment improves endogenous melatonin production and the circadian sleep-wake rhythm.

Materials and methods

Participants

All participants were stable daytime thrice-weekly haemodialysis patients. All had used melatonin 5 mg daily for a minimum period of 12 weeks. None of the par-

ticipants had severe comorbidities, such as class IV heart failure, angina pectoris, pulmonary, psychiatric or neurological diseases, documented sleep apnoea, or blindness. The patients did not use excessive amounts of alcohol, drugs or other sleep medication.

Melatonin rhythm

Melatonin was discontinued for seven days (i.e. stop-week) starting on a haemodialysis day. Starting on days 1, 3 and 7 after discontinuation, six saliva samples were collected at 19:00, 21:00, 23:00, 01:00, 07:00, 15:00h. Sampling of melatonin using saliva was conducted as previously described using a validated method (Russcher et al., 2013).

The primary endpoint was recovery of a normal melatonin rhythm after discontinuation of melatonin in haemodialysis in patients using 5 mg melatonin for at least 12 weeks.

Secondary endpoints were melatonin half-life in hours, area under the curve (AUC) in pg/ml*hour of melatonin, and clearance in ml/min. These parameters were calculated using melatonin saliva concentrations obtained on day 7. In two of the three patients saliva concentrations on days 1 and 3 were above 50 pg/ml and therefore not validated and reliable. Calculations were performed using PkSolver®, a validated add-in of Excel [Office 2013] (Zhang et al., 2010).

Sleep measurements

Sleep was monitored using Actiwatch 2 (Respironics®, Murrysville, USA) actiwatches validated for polysomnography in the haemodialysis population (Koch et al., 2007). Actiwatch Activity & Sleep Analysis version 5.32 was used to score one-minute epochs of actigraphic data as sleep or awake (Oakley, 1997).

Furthermore participants completed two questionnaires at baseline, i.e. vragenlijst ochtend- en avondmensen (VOA), a Dutch validated questionnaire used to classify each participant as a morning or an evening type (Kerkhof, 1984), and the Epworth Sleepiness Scale (ESS), which measures subjective day-time sleepiness and has previously been used in haemodialysis patients (Parker et al., 2003; Russcher et al., 2013).

Sleep-related secondary endpoints were sleep onset latency, which is the time that elapses between “lights off” and sleep onset, sleep efficiency, which is the actual sleep

time divided by time in bed and is a well-recognized measure of sleep quality, and actual sleep time, defined as the total duration of recorded sleep periods. All were calculated according to standardized methods (Carskadon and Rechtschaffen, 2005; Russcher et al., 2013). The medical ethics committee (MEC-U; Medical Research Ethics Committees United in the Netherlands) approved the protocol of the study (NL 43933.100.13) and informed consent was obtained from all the participants.

Results

General outcomes

All the participants were males, had used melatonin for a minimum period of three months and were on chronic haemodialysis. Two haemodialysis patients discontinued melatonin for 7 days and provided saliva samples. A third patient continued to use melatonin until day 6 and discontinued for one day. Relatively low eKt/V values were obtained at day 1 (Table I). These values remained stable throughout the stop-week.

Melatonin rhythm

The melatonin concentrations of case A showed accumulation of melatonin during the day (Figure 1). Insufficient clearance of the exogenous melatonin and high trough levels during the day were seen. Discontinuation of melatonin resulted in recovery of the melatonin rhythm.

In case B, melatonin rhythm was restored after discontinuation. The trough threshold level for DLMO (4 pg/ml) was reached on day 3.

On day 1 case C started with melatonin concentrations above 50 pg/ml and after achieving DLMO his melatonin concentrations decreased. On days 3 and 7 a melatonin rhythm was observed. The melatonin trough threshold level of 4 pg/ml was reached on day 3.

Half-life, AUC and clearance were lower in cases B and C compared with Case A who discontinued exogenous melatonin on day 6 instead of day 1 (Table I).

Sleep parameters

The VOA questionnaire indicated that case A was a distinctly morning person. The actigraphy showed high and

Table I - Participants' characteristics and general outcomes.

	A	B	C
Gender	Male	Male	Male
Age (years)	80	58	72
Weight (kg)	82.3	57.3	110.2
Duration of haemodialysis	56 months	5 months	6 months
Haemodialysis frequency	Every other day in afternoon	3 times weekly in afternoon	3 times weekly in afternoon
Discontinuation melatonin (days)	1	7	7
eKt/V*	0.88	1.17	0.90
Duration of melatonin 5 mg	>12 months	4 months	3 months
t _{1/2} (hours) on day 7	6.2	3.2	1.4
AUC _{0-16h} (pg*h/ml)	913.2	694.9	545.7
Clearance (ml/hour)	0.0055	0.0072	0.0186

* Parameter for dialysis efficiency, the target value in patients on thrice weekly haemodialysis is ≥ 1.2 ; AUC=area under the curve.

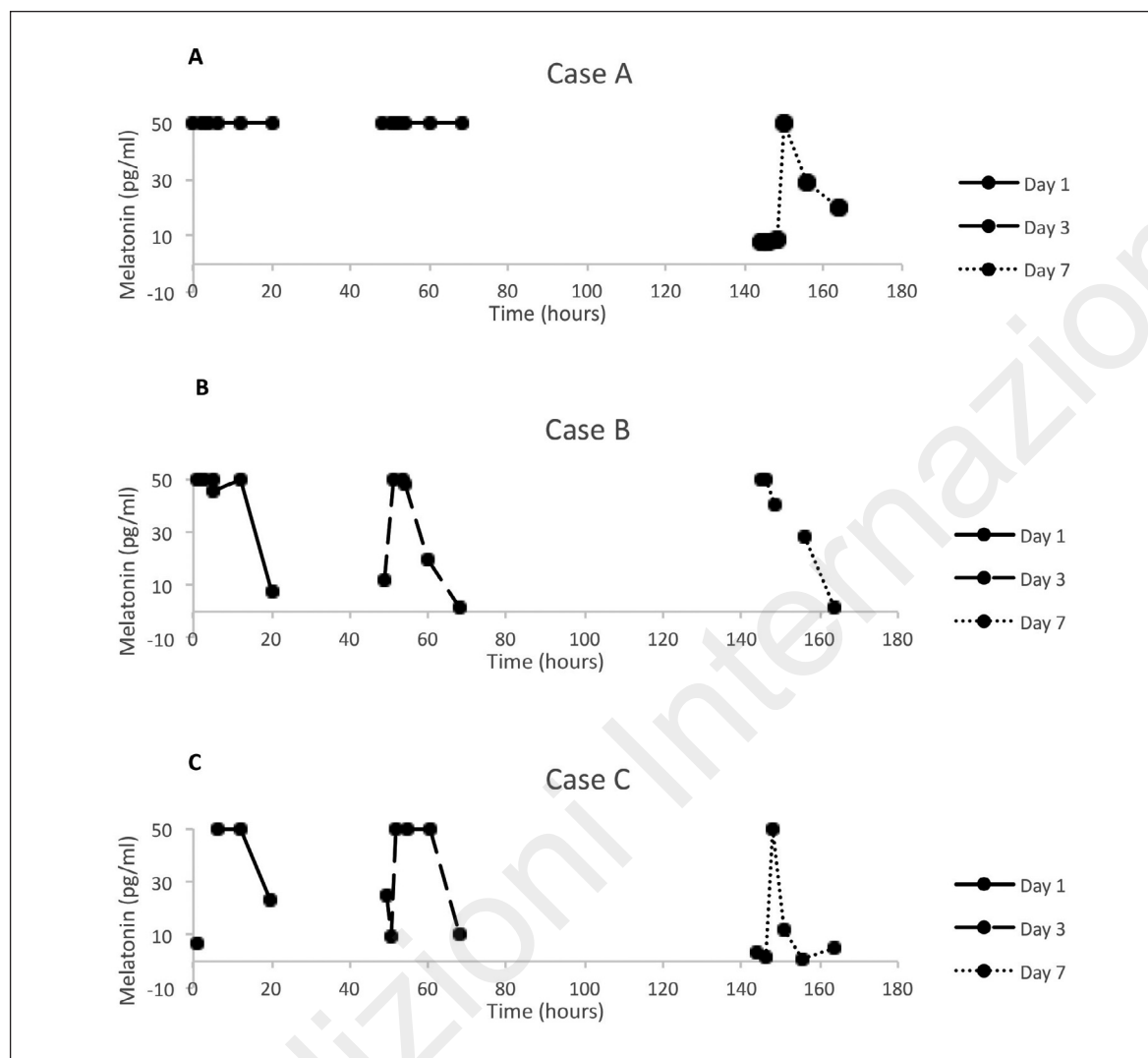


Figure 1 - Melatonin concentrations recorded in the patients at days 1, 3 and 7 (panels A to C). The vertical axis reflects melatonin concentrations in saliva in pg/ml and the horizontal axis the time after discontinuation in hours calculated from day 1. The continuous line represents day 1, the dashed line represents day 3 and the dotted line represents day 7.

erratic sleep onset latency in this participant compared with the other two. A decrease in actual sleep time was observed at the end of the week (after discontinuing melatonin). Figure 2 shows the actual sleep time, sleep efficiency and sleep onset latency traces of the three subjects. Daytime sleepiness did not differ between baseline, day 1 and day 7 in case A.

Case B was also a distinctly morning person, although his bedtime was relatively late, i.e. between 23:30 and 01:00. His actual sleep time was stable during the week. He showed the highest sleep efficiency of all the participants and this was also stable during the week. An increase in sleep onset latency was observed indicating a delayed transition from full wakefulness to sleep.

At baseline the results of the ESS in case C showed mild sleepiness during the day, which changed to normal range during the week. This participant was a distinctly morning person according to the VOA questionnaire. His sleep efficiency was very variable and his ac-

tual sleep time increased slightly during the week. Furthermore, he seemed to show an increased sleep onset latency at the end of the week after discontinuing melatonin for seven days.

Discussion

The main finding of our study is that the circadian rhythm of melatonin returns after discontinuing chronic intake of exogenous melatonin. After three days, the threshold melatonin trough level in saliva (4 pg/ml) was obtained in both the participants who discontinued exogenous melatonin for the full 7 days, resulting in an adequate DLMO phase. Sleep onset latency seemed to increase during the week in all patients. A constant actual sleep time and irregular sleep efficiency were observed in the three participants.

To our knowledge this is the first study to evaluate mela-

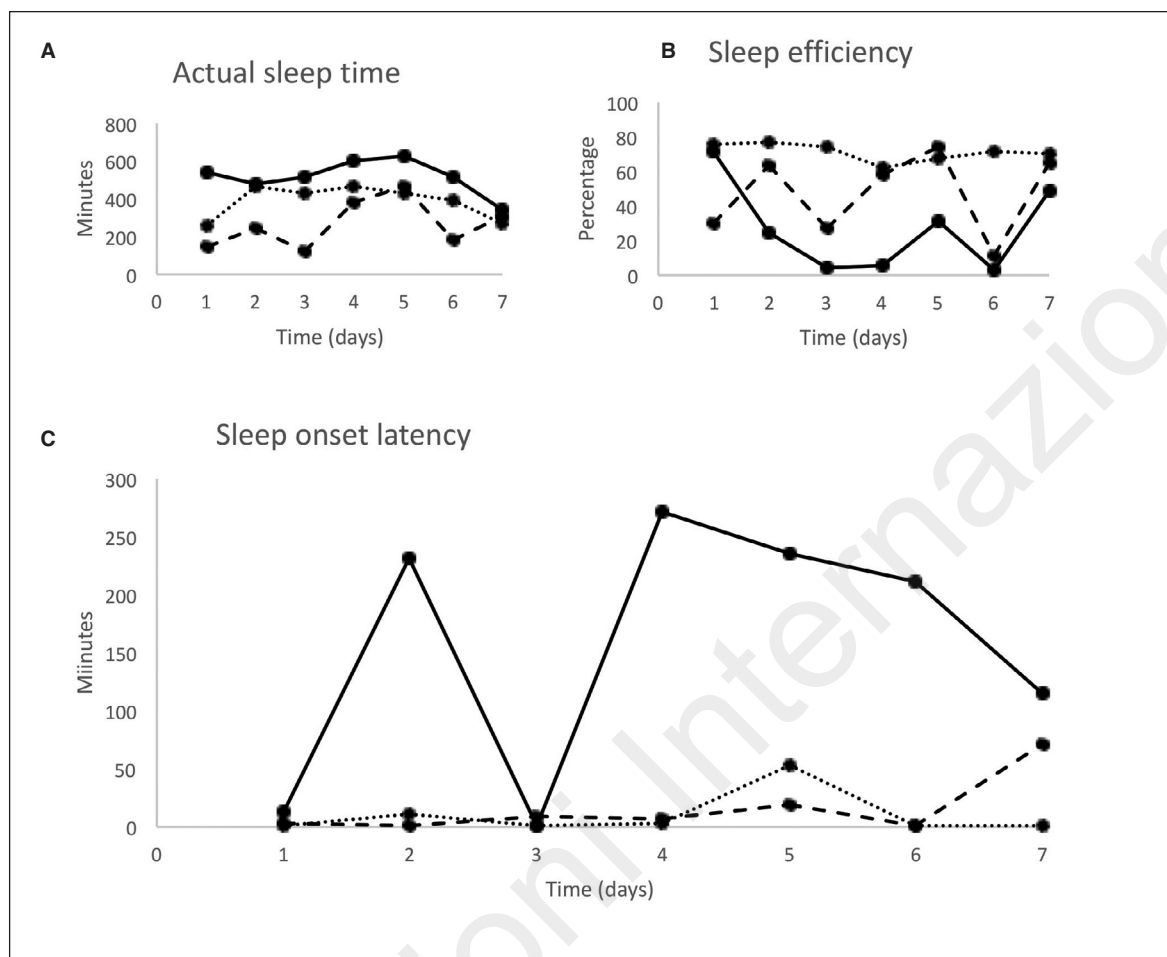


Figure 2 - Sleep parameters of predicted values of actual sleep time in minutes (A), sleep efficiency as a percentage (B) and sleep onset latency in minutes (C). The continuous line represents case A, the dotted line represents case B and the dashed line represents case C.

tonin accumulation and altered circadian rhythm caused by chronic use of the exogenous hormone in haemodialysis patients, and the effects after its discontinuation. An earlier study investigated the long-term effect of exogenous melatonin in haemodialysis patients and found no beneficial effect after six months (Russcher et al., 2013). These findings could be due to constant high melatonin concentrations during the day. Participant A showed no DLMO or adequate clearance of melatonin during the day when using 5 mg melatonin daily. Furthermore effective trough melatonin concentrations were obtained only after discontinuation for at least three days in the other participants.

In the CRIKT study, an AUC of 58.9 pg*h/ml was observed in kidney donors before donation (Russcher et al., 2015). In our study higher AUCs were measured, even at day 7. This could be explained by the accumulation of melatonin after long-term use.

In patients with intellectual disabilities loss of effect of exogenous melatonin has been observed over time as well. Ineffectiveness after several weeks was found to be due to high (> 50 pg/ml) melatonin concentrations during the day. Accumulation of melatonin was hypothesized to be due to polymorphism of the cytochrome

P450 enzyme CYP1A2. However, this hypothesis was based only on melatonin concentrations and their association with discontinuation. It was not confirmed with genetic research. Discontinuing and restarting with a lower dosage resulted in improved sleep parameters (Braam et al., 2010). In a later study by Braam et al. (2013) only 4 out of 15 subjects had single nucleotide polymorphisms and high melatonin concentrations during the day. Our results correspond with these findings in that we also found high melatonin concentrations associated with poor sleep parameters.

Impaired renal function may contribute to the accumulation of melatonin. Melatonin is metabolized by CYP1A and CYP1A2 into inactive 6-sulfatoxymelatonin (Braam et al., 2010). This metabolite and several other glucuronidated metabolites together with two percent unchanged melatonin are excreted by the kidneys. Fifty percent of endogenous melatonin is eliminated during three to four hours of haemodialysis (Lüdemann et al., 2001). Research has shown that after dialysis melatonin concentrations were still higher than control values. Our pharmacokinetic results show higher elimination half-life in the participant who used melatonin until day six, compared with the other two participants. Maybe melatonin

elimination decreases when using daily melatonin in haemodialysis patients. Clearance improved during the week after discontinuing melatonin.

Russcher et al. (2013) proposed that due to the high liposolubility of melatonin it could accumulate in fatty tissue, introducing a physiological slow release mechanism. This could be an explanation for the presence of high melatonin concentrations during the day. However, we were not able to confirm this as participant C (110 kg) had faster clearance and lower AUC than participant B (57 kg).

In actigraphy an underestimation of SOL and sleep time has been found (Sahed, 2011). Although the actiwatch is validated in haemodialysis patients (Koch et al. 2007), this finding should be taken into account when interpreting sleep parameters.

On the basis of the findings in our three cases we hypothesize that a so-called drug holiday, where melatonin is stopped for several days a month, could be a method for regaining melatonin effectiveness by prevention of its accumulation. Drug holidays are used with positive results in children with attention deficit hyperactivity disorder (Ibrahim and Donyau, 2015). In our population, a drug holiday might be helpful when melatonin is no longer effective and sleep parameters decline. The ideal period is difficult to establish. Adequate DLMO should be obtained at least. Therefore trough saliva melatonin concentrations of < 4 pg/ml are necessary (Nagtegaal et al. 1998). In both our participants the threshold was reached at day three after discontinuing. Furthermore the actigraphy results showed a downward trend in sleep parameters at the end of the week. In haemodialysis patients a seven-day drug holiday would probably be the best duration.

Dosage reduction may be another way of preventing accumulation: lowering the dosage to 0.5 mg might have this effect, as previously described in children with intellectual difficulties (Braam et al., 2010).

A large study should be done to obtain more information about sleep and pharmacokinetic parameters in the haemodialysis population. Furthermore, research is necessary to investigate whether sleep parameters improve after a drug holiday, especially to reassure patients. Haemodialysis patients may find it difficult to discontinue their sleep medication due to fear of recurrence of sleep problems.

In conclusion, we demonstrated high melatonin concentrations during the day after chronic exogenous melatonin usage. Discontinuing melatonin seems to result in recovery of the circadian rhythm. Furthermore threshold melatonin trough levels in saliva during the day were obtained.

Further research is necessary to confirm our results in a larger study. Furthermore, research is needed to investigate whether sleep parameters improve after a drug holiday.

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