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Melatonin improves bowel symptoms in female patients with irritable bowel syndrome: a double-blind placebo-controlled study

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SUMMARY

Background: Melatonin is involved in the regulation of gastrointestinal motility and sensation.
Aim: To determine the potential therapeutic effects of melatonin in irritable bowel syndrome (IBS).
Method: Seventeen female patients satisfying the Rome II criteria for IBS were randomized to receive either melatonin 3 mg nocte or identically appearing placebo 1 nocte for 8 weeks, followed by a 4-week washout period and placebo or melatonin in the reverse order for another 8 weeks. Three validated questionnaires – the GI symptom, the sleep questionnaires and the Hospital Anxiety and Depression Scale – were used to assess symptom severity and to compute the IBS, sleep and anxiety/depression scores, respectively.
Results: Improvements in mean IBS scores were significantly greater after treatment with melatonin (3.9 ± 2.6) than with placebo (1.3 ± 4.0, $P = 0.037$). Percent response rate, defined as percentage of subjects achieving mild-to-excellent improvement in IBS symptoms, was also greater in the melatonin-treated arm (88% vs. 47%, $P = 0.04$). The changes in mean sleep, anxiety, and depression scores were similar with either melatonin or placebo treatment.
Conclusions: Melatonin is a promising therapeutic agent for IBS. Its therapeutic effect is independent of its effects on sleep, anxiety or depression.

INTRODUCTION

Irritable bowel syndrome (IBS) is common in the community. Large epidemiological studies from the USA, UK and China have shown that about 11–20% of people in the community experience this condition.[1] The aetiology of IBS is incompletely understood. Sleep disturbance has been suggested as a possible predisposing factor. We previously reported that bowel symptoms and sleep disturbances were more common among night-shift nurses than their regular day shift counterparts and suggested that these disturbances were related to disrupted melatonin rhythms among the shift workers.[2]

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Melatonin is known as the hormone that regulates the sleep-wake cycle. The two major physiological roles of melatonin are regulation of circadian rhythms and induction of seasonal responses to changes in the light–dark cycle. Although the pineal gland is the primary source of melatonin, the hormone is also detected in high concentrations in the gastrointestinal tract (GIT). Animal studies suggest that melatonin is a local regulator of gastrointestinal motility via effects on myoelectric activity of GIT smooth muscle.[3] Its gut regulatory activity is thought to be counterbalanced by its precursor hormone, serotonin (5-HT).[4] Increased 5-HT turnover in the GIT has been blamed for the visceral hypersensitivity and reactivity to stimuli in IBS patients.[5] Melatonin has many potential effects on a sensitized or minimally inflamed gastrointestinal nervous system – the current IBS aetiological hypotheses. These include immune-enhancement of cellular and

humoral systems, and antagonism of the corticoid system.[6] As gut melatonin probably is a major contributor of systemic melatonin concentrations, its effects on the GIT may not be purely related to GIT actions, but may have arisen through actions on the central (e.g. antidepressant effects), sympathetic and parasympathetic nervous systems.[7]

In view of melatonin's known gut regulatory functions, antidepressant and anxiolytic properties, and its potentially beneficial effects on brain gut axis, we hypothesized that melatonin might serve as an effective agent for treating IBS. The aim of this study was to determine if oral melatonin has beneficial effects on bowel symptoms, sleep patterns and psychological profile of female patients with IBS.

SUBJECTS AND METHODS

Subjects

Our subjects comprised 24 non-pregnant and -breast-feeding female patients, aged 41 ± 14 (range 24–66) years old, recruited from the Digestive Disease Clinic of a major teaching hospital. They all fulfilled the Rome II Diagnostic Criteria for IBS[8] and had normal haematological and biochemical indices. In addition, those above 40 years of age also had normal findings on either barium enema or colonoscopy. Patients with previously diagnosed organic gastrointestinal diseases such as inflammatory bowel disease, previous gastrointestinal surgery and concurrent severe systemic diseases including diabetes mellitus were excluded from the study. To avoid potential confounding effects of diagnosis upon efficacy of the trial medications, eligible subjects must have had their diagnosis of IBS made at least more than a month prior to enrolment into the study. Any further investigations were based on clinical indications.

Eighteen age-matched (40.5 ± 14.2, range 21–60 years) healthy female volunteers without bowel symptoms were recruited as normal controls for comparison of salivary melatonin concentrations. All had not been working night-shifts in the preceding 3 months. Both patients and controls were asked not to take any medications known to alter gastrointestinal motility, visceral pain perception and sleep conditions within a month before and during the study. These include all psychoactive drugs such as sedatives and antidepressants. During the study, all subjects were also specifically told to have a normal diet and to avoid long distance travel.

Written informed consent was obtained from all the subjects before their participation in the study. The hospital research and ethics committee approved the study protocol.

Questionnaires

Each patient underwent a detailed history and physical examination and was asked to complete two reliable and validated questionnaires: (i) the IBS Symptoms Evaluation Score Questionnaire (IBSSESQ), which included a Sleep Questionnaire based on the Epworth Sleepiness Scale,[9] and (ii) the Hospital Anxiety and Depression Scale (HAD). The IBSSESQ questionnaire, the HAD scale, and the Sleep and Bowel Diary had all been previously validated and used in Singapore to assess the frequency and severity of gastrointestinal symptoms, quality of life, psychological profile and sleep disturbances, respectively.[2,10] The IBSSESQ questionnaire assesses the frequency and severity of the abdominal pain, severity of abdominal distension, frequency of defecation, stool type, frequency and severity of abnormal sensation of defecation, sleep, well-being and somatic pain. Responses to the questions were rated in 0.5 increments from zero to three (0 = not at all; 3 = severe). The sleep questionnaire consisted of eight self-rated questions, which evaluated a variety of daytime situations when one may doze off to sleep and rating is on a scale of zero to three (0 = no chance of dozing; 1 = slight chance of dozing; 2 = moderate chance of dozing; and 3 = a high chance of dozing). A score of eight or more was considered to indicate sleepiness. For the HAD scale, the responses to questions were rated in increments of one, from zero to three (0 = not at all; 3 = severe). The sums of symptom severities were used to compute the IBS symptom score, the anxiety/depression scores and the sleep disturbance score, respectively.

Each subject was also asked to keep a Bowel and Sleep Diary for at least 2 weeks, while discontinuing any medication that could affect gastrointestinal motility and visceral pain perception. Based on the data obtained from the diary, they were categorized into those who had constipation predominant symptoms and diarrhoea predominant symptoms. Only patients who had active IBS symptoms at the time of enrolment and whose IBS symptom score consisted of at least a moderate severity

on at least one of IBS symptoms were eligible for the study.

Melatonin preparation

The melatonin and placebo tablets were custom-made (Little Pharmaceutical Pte Ltd, Singapore) using material that was imported (JOVA Chemie GmbH, Germany). The fast release tablet comprised melatonin, starch, lactose, carboxymethylcellulose, sodium benzoate and magnesium stearate. All tablets manufactured for this trial were tested and found to be in compliance with established B.P.98 standards for tablets. The assay results of three batches of tablets concluded that each tablet contains 3 mg melatonin ±10% of stated value (Report from Little Pharmaceutical Pte Ltd).

Treatment randomization

Each patient was randomized, by way of tossing a coin, to receive either melatonin 3 mg nocte or an identically appearing placebo tablet nocte for 8 weeks. During the treatment period, patients were asked to complete the Bowel and Sleep Diary daily.

At the end of the 8 week, patients were interviewed to assess symptom status using the IBSSESQ Questionnaire and the HAD Scale. The Bowel and Sleep Diary was reviewed, and drug accountability, adverse effects and use of concurrent medications were recorded as well at the same visit. If patients had returned more than the equivalent of 3 days' medications, they were considered poor compliers. The patients were also asked to rate globally their bowel and sleep symptoms using the following grades: poor, nil, mild, good and excellent. Poor means deterioration of their symptoms, nil means no change in their symptoms, mild means clear but limited improvement in their symptoms, good means considerable overall improvement in their symptoms and excellent means complete or near-complete disappearance of their symptoms. Patients who had achieved mild, good and excellent improvement in their global symptom evaluation following treatment with either placebo or melatonin were considered as responders. The colonic transit measurement was repeated to assess changes in colonic transit times (CTTs).

A 4-week washout period followed, and patients were then asked to take placebo or melatonin in the reverse order for another 8 weeks. Prior to and at the end of the last treatment phase, patients repeated the IBSSESQ Questionnaire, the HAD Scale, the global symptom evaluations and the colonic transit studies. The Bowel and Sleep Diary was kept throughout the study period. To avoid potential bias, rescue medications for IBS symptoms were not allowed during the washout period.

Colonic transit measurement

In addition to the questionnaires, all patients undertook a colonic transit study a week before and after melatonin treatment. Concomitant use of motility agents was prohibited for at least 2 weeks prior to the study. The colonic transit study was performed using a blue dye method as described by Menzies *et al.*[11] The method was internally validated against an established radio-opaque method[12] and the standard Bristol Stool Form Scale tests using a series of 14 normal volunteers. After an overnight fast, each patient ingested one dye capsule (food colour, non-toxic and non-absorbable; F.D. & Blue No.1 Brilliant Blue F.C.F. – Pronk Davis & Rusby Ltd, London) and was told to monitor for the first discharge of blue coloured stool. Colonic transit time was evaluated as the time interval between ingestion of the capsule and the discharge of the first blue-stained stool (range in normal controls: 7.7–8.8 h).

Saliva melatonin levels

One millilitre of saliva was collected from each IBS patient at 9:30 AM at fasting status prior and after each treatment and stored at −20 °C. Saliva melatonin levels were measured using an ELISA method (Buhlmann Laboratories, Basel, Switzerland; Cat-No: B-EKDSM-CONSET). All samples were coded and the investigator did not know the names of the samples until the measured results were obtained and the trial code broken.

Data and statistical analysis

The data generated from the assessments at four-time points prior to and after the two treatment phases were input into the computer before the randomization code was broken. All patients who gave consent to participate in this study, who were randomized to a treatment group, and completed both the treatment phases were considered to be eligible for the efficacy and safety analyses. However, patients were included in the final efficacy analysis only if they met all of the following

criteria: they must have had a baseline assessment; they must have had a post-therapy assessment; they must not have had an indeterminate post-therapy response and they must not have had been poor compliers.

The mean scores before treatment minus those after treatment with either melatonin or placebo were tested using histogram and normality of distribution. Almost all the mean score differences were normally distributed. The differences that were not normally distributed were normalized by log transformation (base 10). The General Linear Model was used to analyse the differences of mean scores and to test whether there was a carry-over effect on the differences of each mean score between the group who received melatonin first (group A) and those patients who received placebo first (group B). A carry-over effect is considered to be present in a cross-over trial when one or both of the study medications taken during the first drug period exerted residual biological effects during the second drug period.[13] The mean global evaluation of IBS symptoms was expressed in percentage and analysed by the chi-squared test. The baseline of IBS score, sleep score, anxiety and depression score were analysed by Student's *t*-test and Mann–Whitney *U*-test. Saliva melatonin results were analysed by Wilcoxon Signed Rank Test and Mann–Whitney *U*-test. Two-tailed *P*-values of <0.05 was taken as the level of statistical significance in all analyses, which were performed with SPSS for Windows version 10.

RESULTS

Subject characteristics

Amongst the 24 patients, 12 were randomized to receive melatonin first (Group A) and the rest placebo first (Group B). One patient in Group A withdrew because she was too busy to return for the follow-up visits, one in Group A and four in Group B withdrew after the first course of treatment because of lack of beneficial effects. The other patient in group B dropped out from the study because her diarrhoea worsened while she was given placebo. Of the remaining 17 (71%; 10 in Group A, 7 in Group B) who were eligible for the final efficacy and safety analyses, seven had constipation predominant symptoms and the rest diarrhoea predominant symptoms. All 17 showed excellent compliance with all of them taking all the tablets during the entire treatment duration.

Groups A and B were well matched with respect to age, race, duration of IBS symptoms, baseline IBS symptom scores, baseline sleep disturbance scores, baseline anxiety scores, baseline depression scores, baseline well-being scores and baseline CTTs (Table 1). It is notable that our IBS patients had sleep scores that were <8, indicating that they did not have disrupted sleep.

The General Linear Model was employed to analyse for possible carry-over effects between Groups A and B. The results, showing no significant difference in the changes of IBS mean scores ($P = 0.7$), sleep disturbance mean scores ($P = 0.8$), anxiety mean scores ($P = 0.35$), depression mean scores ($P = 0.45$), global IBS symptom evaluation mean scores ($P = 0.76$), global sleep evaluation mean scores ($P = 0.4$) and CTT mean scores ($P = 0.09$) between Groups A and B, indicated the absence of carry-over effects in these parameters. The data of Groups A and B were, therefore, pooled for subsequent analyses of the differences of efficacy between treatments with active and placebo medications.

The two treatment groups were well matched with respect to age, race, duration of IBS symptoms, baseline IBS symptom scores, sleep disturbance scores, anxiety

Table 1. Baseline characteristics of the two treatment groups

Characteristics	Normal range	Active ($n = 17$)	Placebo ($n = 17$)	*P*	95% CI
Mean age (s.d.)	–	41.2	41.2	1.0	−9.4–9.4
No. of Chinese (%)	–	82%	82%		
Mean duration of symptoms (s.d.), year	–	2.9 (1.3)	2.9 (1.3)	1.0	−9.4–9.4
Mean baseline IBS score (s.d.)	0–8	11.1 (4.2)	11.8 (3.4)	1.0	−0.9–0.9
Mean baseline sleep score (s.d.)	0–8	5.4 (1.8)	5.1 (1.9)	0.69	−1.5–1.0
Mean baseline anxiety score (s.d.)	0–7	7.7 (3.8)	7.7 (4.7)	1.0	−3.04–3.04
Mean baseline depression score (s.d.)	0–7	6.9 (3.2)	6.4 (3.5)	0.6	−1.9–2.7
Mean baseline well-being score (s.d.)	0–1	1.1 (0.4)	1.3 (0.6)	0.5	0.2–0.5
Mean baseline CTT (s.d.), days	8 h	1.9 (1.5)	1.3 (0.9)	0.1	−1.6–0.2

Table 2. Changes in mean symptom scores after treatment with either melatonin or placebo

Scores	Melatonin	Placebo	*P*-value
Change in mean (s.d.) IBS symptom scores	3.9 (2.6)	1.3 (4.0)	0.037
Change in mean (s.d.) sleep disturbance scores	1.7 (2.1)	1.1 (1.9)	0.41
Change in mean (s.d.) anxiety scores	0.94 (3.9)	1.4 (2.6)	0.9
Change in mean (s.d.) depression scores	1.5 (2.6)	1.1 (2.8)	0.7
Change in mean (s.d.) well-being scores	0.26 (0.6)	0	0.4
Change in mean (s.d.) global evaluation of IBS symptom scores	1.3 (0.6)	0.6 (1.0)	0.1
Change in mean (s.d.) global evaluation of sleep disturbance scores	1.3 (0.8)	1.0 (1.2)	0.3
Change in mean (s.d.) CTTs, days	0.94 (1.2)	0.28 (0.8)	0.2

Table 3. The percent response of patients treated with melatonin and placebo

Degree of response	Melatonin no. (%)	Placebo no. (%)
Worse	0	1 (5.9)
No change	2 (11.8)	8 (47.1)
Mild improvement	8 (47.1)	3 (17.6)
Good improvement	6 (35.3)	5 (29.4)
Excellent improvement	1 (5.9)	0
Total	17	17

scores, depression scores, well-being scores and CTTs (Table 1).

IBS symptoms

The improvement in mean ± s.d. IBS symptom score was significantly greater after treatment with melatonin (3.9 ± 2.6) than with placebo therapy (1.3 ± 4.0, $P = 0.037$) (Table 2). Percent response rate, *a priori* defined as percentage of subjects achieving mild-to-excellent improvement in global evaluation of their IBS symptoms, was also greater in the melatonin-treated arm (88.2%) than in the placebo-treated arm (47.1%, $P = 0.04$) (Table 3). The changes in mean sleep disturbance scores, mean anxiety scores, mean depression scores, mean well-being scores, mean global evaluation of IBS symptom scores, mean global evaluation of sleep scores were similar after treatment with either melatonin or placebo (Table 3).

The General Linear Model established the absence of carry-over effects in individual bowel symptoms included in the IBS symptom score by showing no significant differences in the changes of abdominal pain mean scores ($P = 0.9$), abdominal distension mean scores ($P = 0.7$), abnormal sensation of defecation mean scores ($P = 0.9$), stool consistency mean scores ($P = 0.6$) and frequency of defecation mean scores ($P = 0.7$) between Groups A and B. It was then used to assess which individual bowel symptom was improved by the melatonin treatment. Compared with the placebo therapy, melatonin treatment resulted in a greater improvement in abdominal distension ($P = 0.02$), abdominal pain (pain intensity and frequency, $P = 0.045$) and abnormal sensation of defecation (rush, strain and incomplete feeling; $P = 0.04$) (Table 4). Stool consistency and frequency did not differ after treatment with either melatonin or placebo. As only two patients had mucus per rectum, this symptom was not further analysed.

Colonic transit times

Although the mean ± s.d. CTT measured by blue dye method appeared to be more prolonged after melatonin treatment (34.1 ± 34.9 h) than after placebo treatment

Table 4. Changes in mean scores of individual IBS symptoms after treatment with either melatonin or placebo

Scores	Melatonin	Placebo	*P*-value
Change in mean (s.d.) abdominal pain scores	1.17 (1.2)	0.47 (1.6)	0.045
Change in mean (s.d.) abdominal distension scores	0.62 (0.6)	0.12 (0.7)	0.019
Change in mean (s.d.) abnormal sensation of defecation scores	1.15 (1.1)	0.24 (1.3)	0.04
Change in mean (s.d.) stool consistency scores	0.45 (0.7)	0.41 (0.9)	0.9
Change in mean (s.d.) frequency of defecation scores	−0.7 (1.1)	−0.9 (1.4)	0.7

(15.4 ± 28.1 h), the difference did not reach statistical significance. Similarly, there was no statistically significant difference in the mean change in CTTs after treatment with either melatonin or placebo (Table 2).

Salivary melatonin levels

The IBS patients' mean ± s.d. baseline saliva melatonin levels (2.3 ± 3.5 pg/mL) were significantly lower than those of 18 age-, sex-matched normal controls (5.9 ± 6.6 pg/mL; $P < 0.001$). After melatonin treatment, the mean ± s.d. saliva melatonin levels of IBS patients increased significantly (8.3 ± 7.5 pg/mL, $P < 0.001$) compared with the baseline value. By Spearman's correlation coefficient test, there was a trend towards a negative correlation between saliva melatonin and abdominal pain ($r = -0.47$, $P = 0.075$). There was also a negative correlation between saliva melatonin and total bowel symptom score; abnormal sensation of defecation score; total sleep score; anxiety score; and depression score. However, the *P*-values of all these correlations did not reach statistical significance. By linear regression test, saliva melatonin was found not to be an independent predictor of abdominal pain.

Adverse effects of treatment

Of all the patients who completed the study, only three complained of symptoms possibly attributable to 'side effects of the treatments'. One complained of skin rash and another complained of vaginal pruritus while they were in the placebo arm. One complained of daytime sleepiness with both the placebo and active treatments. None had to stop treatments because of these symptoms.

DISCUSSION

The results of the present study showed that an 8-week course of oral melatonin at a dose of 3 mg/day was effective in improving bowel symptoms in female patients with IBS. The beneficial effects of melatonin were most marked in symptoms such as abdominal pain, abdominal distension and abnormal sensation of defecation. The frequency of bowel movement and stool consistency was not affected by the use of melatonin. Similarly, melatonin did not appear to influence the CTTs. At the prescribed dose, melatonin did not have significant effects on the sleep pattern or psychological profile of patients with IBS. These results suggest that melatonin probably improved IBS symptoms by modifying visceral pain perception rather than influencing gut motility, sleep pattern, or psychological well-being in patients with this condition.

The results further suggest that melatonin may have a peripheral anti-5-HT-like effect. 5-HT is thought to be a likely contender in the induction and maintenance of visceral hypersensitivity associated with IBS. 5-HT, acting mostly at 5-HT3 or 5-HT3-like receptors, enhances the sensitivity of visceral neurons projecting between the gut and the central nervous systems. However, 5-HT, acting at 5-HT4 receptors, promotes the sensitivity of enteric neurones that react to luminal stimuli.[5] The GIT may produce melatonin that binds to sites in the various segments of the GIT and acts as autocrine and paracrine neurotransmitter.[14,15] Such melatonin is known to be a local regulator of gastrointestinal motility and sensitivity.[16] Its gut regulatory activity is thought to counterbalance that of its precursor hormone, 5-HT.[4] By antagonizing the visceral sensory enhancing effects of 5-HT, melatonin reduces visceral sensitivity. However, we cannot preclude the possibility of centrally mediated effects. As previously discussed, melatonin may exert its effects through the central, sympathetic and parasympathetic nervous systems[7] and also act via enhancement of cellular and humoral immune systems, as well as through corticoid antagonism.[6]

It is well documented that melatonin has a sleep promoting effect and some mood modifying properties.[17–23] However, our study showed that melatonin did not improve the sleep pattern of patients with IBS. It also showed that melatonin did not have significant anxiolytic and antidepressant effects in these treated patients. One possible reason to explain this is that patients with IBS may exhibit a high placebo response, thus masking any possible beneficial effects of melatonin compared with placebo. It is also possible that a higher dose of melatonin may be required for its sleep promoting, anxiolytic and antidepressant effects.

The strengths of this study include its randomized, double-blind, placebo controlled design, its use of reliable and locally validated interview instruments and the excellent adherence to protocol by the study subjects. We initially planned to perform a parallel rather than a cross-over study. Doing the former would have required a total of 140 patients to be randomized to both the arms. However, a 2-month pilot study saw

only four patients being recruited. Recognizing the recruitment difficulty, we changed the study design to a cross-over trial. It could be argued that by changing the study design to that of a cross-over, the results obtained might have been less than credible as the responses in the second treatment period could have been influenced by the responses in the first period. However, this possibility seems unlikely as the improvement in mean IBS symptom scores and individual mean scores of IBS symptoms among the treated patients remained even after eliminating the carry over effects using the General Linear Model analysis.

A previous study showed that for the fast release melatonin, physiological dosage 0.5 mg/day is as good as pharmacological dosage 5 mg/day for improving the symptoms of jet lag such as self-rated sleep quality, shortened sleep latency, and reduced fatigue and daytime sleepiness.[24] There is no point in giving a higher pharmacological dose if the physiological dose or lower pharmacological dose works well to improve symptoms. So, we chose a 3 mg/day dosage for treating IBS. The patients were asked to take melatonin at bedtime in order to make melatonin peak occur in the body close to nature melatonin circadian rhythm. Because most brands of melatonin products available on the market are food level and low quality products, we got a local pharmaceutical company to custom-make the pharmacological grade melatonin for our trial study.

It has been previously reported that saliva melatonin was highly correlated to the blood melatonin.[25] Our results showed that IBS patients had significant lower saliva melatonin than normal controls. Abnormal melatonin levels may have caused gut hypersensitivity and reactivity and their attendant bowel disturbances. After melatonin treatment, the saliva melatonin levels of IBS patients increased significantly from their baseline levels. This demonstrated that the trial melatonin had a good bioavailability and the dosage administered was adequate for treating IBS patients.

Melatonin is available over the counter in many countries in the world, including the USA. Its ready availability for public use is mainly because of its safety and lack of serious adverse reactions. In the present study, we used an oral fast release melatonin at a dose of 3 mg/day for 8 weeks and confirmed that it had few, if any, adverse effects. However, in the light of recent findings on possible centrally mediated effects of melatonin, including those on the immune function, safety of the long-term use of this medication should be evaluated.[6]

In summary, the present study showed that oral melatonin is a promising therapeutic agent for the treatment of IBS. It is most effective in relieving abdominal pain, abdominal distension and abnormal sensation of defecation in female patients with IBS. However, further studies are required to confirm the efficacy and long-term safety of melatonin before it can be recommended for routine clinical use.

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