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Influence of melatonin on symptoms of irritable bowel syndrome in postmenopausal women

Wpływ melatoniny na objawy zespołu jelita nadwrażliwego u kobiet w okresie pomenopauzalnym

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Abstract

Introduction: Melatonin (MEL) exerts beneficial effects on the gut partly by myorelaxative properties upon the smooth muscle. Its secretion decreases with age, particularly in postmenopausal women.
This study was aimed at evaluating the effect of MEL on the symptoms of irritable bowel syndrome (IBS) in this group of patients.
Material and methods: The investigations were carried out in 80 postmenopausal women, aged 48–65 years, divided into two equal groups, diagnosed according to Rome Criteria III: i.e. patients with IBS with constipation predominant (IBS-C), and patients with IBS with diarrhoea predominant (IBS-D). The control group (C) included healthy women aged 46-65 years. In all subjects, 6-sulfatoxymelatonin (6-HMS) concentration urine was measured using ELISA assay. Patients in both groups over the course of six months were given melatonin (at a dose of 3 mg fasting and 5 mg at bedtime) or a placebo (double blind trial). Disease activity was evaluated after two, four and six months, using a ten-point scale to assess the main somatic symptoms: visceral pain, abdominal bloating, etc.
Results: The amounts of 6-HMS urine excretion (μg/24h) were: C 11.4 ± 3.0, IBS-C 10.2 ± 3.2, IBS-D 14.0 ± 6.3 ($p < 0.05$).
Correlation between values of symptoms score and contrary excretion of 6-HMS: IBS-C $r = -0.714$, IBS-D $r = 0.409$.
After six months in the IBS-C group, the intensity of visceral pain and abdominal bloating had decreased in 70% of patients ($p < 0.01$) and constipation in 50% of patients ($p < 0.05$). Beneficial changes in the IBS-D group were noted in 45% of patients, but this was not better compared to the placebo.
Conclusions: Melatonin can be used as part of the treatment of IBS, particularly in patients with constipation-predominant IBS.
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Key words: *menopause, irritable bowel syndrome, melatonin, 6-sulfatoxymelatonin*

Streszczenie

Wstęp: Melatonina (MEL) korzystnie wpływa na przewód pokarmowy, między innymi poprzez relaksujące działanie na mięśnie gładkie. Jej wydzielanie zmienia się wraz z wiekiem, szczególnie u kobiet w okresie pomenopauzalnym. Celem pracy była ocena wpływu melatoniny na objawy zespołu jelita nadwrażliwego w tej grupie kobiet.
Materiał i metody: Do badania włączono 80 kobiet, w wieku 48–65 lat. Zgodnie z Kryteriami Rzymskimi III wyodrębniono grupę z zaparciową postacią jelita nadwrażliwego (IBS-C, n = 40) i z biegunkową postacią tej choroby (IBS-D, n = 40). Grupę porównawczą (C) stanowiło 30 kobiet zdrowych, w tym samym wieku.
U wszystkich określono dobowe wydzielanie siarczanu 6-hydroksymelatoniny (6-HMS) z moczem.
Pacjentki w obu grupach przyjmowały przez 6 miesięcy melatoninę (3 mg rano i 5 mg wieczorem) lub placebo. W 2,4 i 6 miesiącu oceniono nasilenie dolegliwości (bóle i wzdęcia brzucha oraz deregulację wypróżnień), używając wizualnej 10 stopniowej skali.
Wyniki: Wydalanie 6-HMS z moczem (μg/24 h) wynosiło odpowiednio w grupach: C — 11,4 ± 3,0, IBS-C — 10,2 ± 3,2, IBS-D — 14,0 ± ± 6,3 ($p < 0,05$).
Stwierdzono korelację między nasileniem objawów a wydzielaniem 6-HMS: ujemną IBS-C ($r = -0,714$), a dodatnią w grupie IBS-D ($r = 0,409$).
Po 6 miesiącach używania melatoniny w grupie IBS-C bóle i wzdęcia brzucha zmniejszyły się u 70% pacjentek, a zaparcia u 50% pacjentek. W grupie IBS-D poprawę uzyskano u 45% pacjentek, a wyniki nie różniły się znacząco od tych w grupie przyjmującej placebo.
Wnioski: Melatonina może być stosowana w skojarzonej terapii IBS, szczególnie w postaci z zaparciami.
(Endokrynol Pol 2013; 64 (2): 114–120)

Słowa kluczowe: *menopauza, zespół jelita nadwrażliwego, melatonina, siarczan 6-hydroksymelatoniny*

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Introduction

Irritable bowel syndrome (IBS) is a functional disease of complex pathogenesis. Genetic and environmental predispositions, chronic stress and depression are listed among IBS aetiological factors [1]. Brain-gut axis dysfunction is affected by various factors [2, 3]. Both elements of this axis can be responsible for IBS symptoms. In CNS, as well as in the gastrointestinal (GI) tract, there are a lot of the same neurotransmitters and hormones and their receptors which play a major role in the regulation of gastrointestinal tract functions [4].

Among hormones, melatonin is the one which is of importance. It is secreted by the pineal gland in circadian rhythm, regulated mainly by the effect of light [5]. Enterochromaffin cells (EC), widely distributed along the whole GI tract, are a markedly rich source of this indoleamine [6]. Melatonin is secreted from the GI tract under the effect of different stimuli, including nutritional ones, and it fulfils various enteroprotective functions.

Melatonin manifests strong antioxidant and anti-inflammatory [7–9] activity. Moreover, it regulates intestinal motility. The results of numerous studies have pointed to its inhibitory effect on smooth muscle motor activity [10]. This effect can be induced by direct stimulation of specific receptors [11], regulation of the activity of exchange channels Ca^{2+}/K^{+} in cells [11, 12] as well as indirectly by visceral nervous system [13, 14]. This hormone blocks nicotinic acetylcholine receptors in submucosal plexus neuronal endings and activates afferent fibres of the vagus nerve through the increase of CCK release and activation of CCK1R/CCK2R [15].

Harlow and Weekly [16] as well as Bubenik [17] showed that melatonin's myorelaxative effect is directly proportional to the basic spontaneous tone and amplitude of intestinal contractions in rats. In another study, Drago et al. [18] observed that melatonin in low doses accelerated, and in high doses slowed, the intestinal transit in the experimental models in animals. It also exerts a modulating effect on visceral sense [19].

Visceral hypersensitivity is a major element in IBS pathogenesis. The lowered pain threshold is observed in most patients with this disease which makes pain appear even with normal intestinal motility.

The above properties of melatonin, recognised predominantly in experimental studies, have been attempted to be used in medical practice.

A lot of clinical evaluations have pointed to the beneficial effect of melatonin in IBS therapy. Song et al. [20] described advantageous results of melatonin therapy (3 mg in the evening) as quickly as after two weeks, particularly decreased rectal sensitivity and reduced abdominal pain. Saha et al. [21] observed that the application of melatonin in an evening dose of 3 mg for eight weeks improved significantly the IBS patients' quality of life compared to the group receiving a placebo.

Lu at al. [22] also confirmed the efficacy of an evening dose of 3 mg of melatonin in women with IBS. In this group, the prevalence of abdominal pain and distension as well as abnormal urge to defecate markedly decreased.

Considering also the results obtained by Radwan et al. [23] i.e. a significant reduction of urinary 6-HMS excretion both in patients with diarrhoea-predominant and constipation-predominant IBS, it appears that

Table I. *Characteristics of subjects enrolled on the study*
Tabela I. *Charakterystyka kliniczna osób włączonych do badania*

Feature/parameters	Healthy subjects	Patients with IBS-C	Patients with IBS-D
Number	30	40	40
Age (years)	36.5 ± 5.2	56.1 ± 6.2	54.5 ± 6.6
BMI	22.3 ± 1.2	23.4 ± 0.8	21.0 ± 0.9
FSH [UI/mL]	9.2 ± 6.0	88.5 ± 19.8	101.3 ± 512.6
Oestradiol [pg/mL]	112.3 ± 41.5	10.6 ± 2.9	13.0 ± 3.0
AST [U/L]	19.8 ± 5.1	23.6 ± 4.7	20.9 ± 5.8
ALT [U/L]	19.8 ± 5.1	18.8 ± 3.9	21.0 ± 5.1
GGTP [U/L]	27.2 ± 7.0	29.4 ± 9.5	30.1 ± 8.3
Ammonia [μg/dL]	29.8 ± 9.2	33.6 ± 10.2	26.7 ± 11.2
GFR [mL/min]	109.0 ± 9.7	105.4 ± 8.8	98.8 ± 7.5

BMI — body mass index; FSH — follicle-stimulating hormone; AST — aspartate aminotransferase; ALT — alanine aminotransferase; GGTP — gamma-glutamyl transferase; GFR — glomerular filtration rate

low secretion of melatonin may be one of the causes of this disease, and this hormone can be administered substitutionally.

Such a conclusion should be drawn cautiously because in an earlier study Stępień et al. [24] found the highest melatonin secretion in both forms of IBS compared to healthy subjects. This divergence could result from differences in the selection of patients for the examinations, also as regards gender and age.

Furthermore, the psychoemotional state of the patients and the melatonin dose recommended for therapeutic purposes are also of importance.

Taking into account these reservations, our studies were undertaken in a homogeneous group of postmenopausal women considering urinary 6-HMS excretion as the exponent of melatonin synthesis and metabolism.

The aim of our study was the evaluation of the influence of melatonin on the symptoms of irritable bowel syndrome in postmenopausal women.

Material and methods

Eighty women were enrolled in this study, aged 48–65 years (mean 55.3 ± 6.4), with irritable bowel syndrome (IBS) and in the postmenopausal period. The time that had passed since the last menstruation varied from 2–14 years. Oestrogen deficit was observed in all patients: mean serum concentration of oestradiol-17β was 11.6 ± 3.0 pg/mL, and increased FSH concentration to 94 ± 11.0 IU/dm^3. The control group (C) included 30 premenopausal women, aged 31–45 years (mean 36.5 ± 5.2) without complaints or GI tract diseases.

Based on the Rome III criteria [25], 40 women with constipation-predominant IBS (IBS-C) were distinguished and 40 with diarrhoea-predominant IBS (IBS-D).

In all the subjects enrolled in the study, endoscopy examinations of the upper and lower parts of the intestinal tract were performed, histopathology of the colon mucosa was obtained, abdominal ultrasound was performed, as well as the following laboratory tests: blood cell count, CRP, glucose, electrolytes, bilirubin, urea, creatinine, cholesterol, triglycerides, TSH and activity of the following enzymes: AST, ALT, GGTP, FA, amylase and lipase.

In patients with IBS-D, additionally parasitological and bacteriological stool examinations, biopsy and histological analysis of the small bowel mucosa were performed. Patients with organic, metabolic and psychiatric diseases, as well as those on long-term treatment with pharmacological agents, and cigarette smokers, were excluded from the study.

Seven days prior to the evaluations, all medications were withdrawn and the same diet was recommended in all subjects, particularly with a similar daily amount of products rich in L-tryptophan. On the day of the study, the subjects remained in the room with only a red light from 9.00 p.m. till 7.00 a.m. and the same liquid diet was administered (Nutridrink, Nutrica, Netherlands) in the amount of 3 × 400 ml of the caloric value of 1,800 kcal, and 1,500 mL of isotonic still water. At the same time, the 24 h urine collection was performed. Urine was kept at +4°C. Immediately after the end of 24-hour collection, the volume of urine was measured, centrifuged and the samples were frozen at –70°C. The concentration of 6-HMS in the urine was measured by the ELISA method applying IBL antibodies (RE-54031, Immunological Laboratories) and Expert 99 MicroWin 2000 reader (Biogenet). The obtained results were converted from μg/mL to μg/24 h.

After diagnostic investigations, melatonin was administered to 20 patients in both groups in a morning dose of 3 mg and an evening dose of 5 mg and 20 patients received a placebo in the same dose regimen, in a double blind procedure for six months. The patients kept an observation diary in which they noted the intensification of three main somatic ailments: visceral pain, abdominal bloating and constipation or diarrhoea. To evaluate the effect of melatonin or placebo on the clinical picture of the disease, a ten-point Visual Analogue Scale (VAS) was used distinguishing mild (1–4 points), moderate (5–7 points) and severe (8–10 points) stages.

The study was approved by the Ethical Committee of the Medical University in Lodz (No.: RNN 238/05/ /KB) and the enrolled patients signed written consent.

The data was analysed statistically applying the Kruskal-Wallis and Mann-Whitney and chi-square tests using Statistica-Microsoft Co. software.

Results

The urinary 6-HMS excretion in the control group of women without GI tract ailments was 11.4 ± 3.0 μg/24 h (Fig. 1).

A similar result was obtained in the group of women with IBS-C — 10.2 ± 3.2 μg/24 h ($p > 0.05$). In the moderate stage of this disease in 19 women, 6-HMS excretion was 13.5 μg/24 h, whereas in the severe stage it was significantly lower in 21 women — 9.3 ± 1.7 μg/24 h.

In IBS-D, the urinary 6-HMS excretion was higher than in healthy women and it was 14.0 ± 6.3 μg/24 h ($p < 0.01$). This difference was particularly pronounced in the group of 18 women with severe IBS-D — respectively 11.42 ± 3.03 and 18.97 ± 5.70 μg/24 h.

We noted a negative correlation between values of symptoms score and contrary excretion of 6-sulfatoxymelatonin in patients with IBS-C; value of correlation

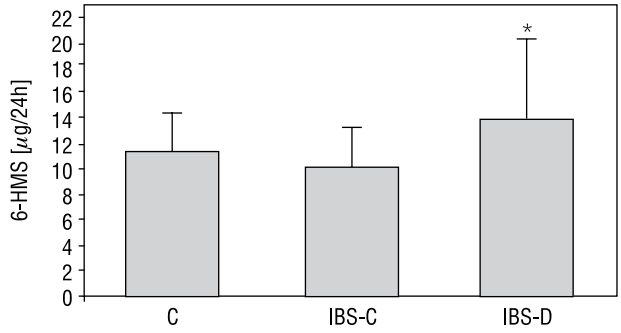

Figure 1. *6-sulfatoxymelatonin (6-HMS) urinary excretion in healthy subjects (C) and in patients with irritable bowel syndrome with constipation (IBS-C) and diarrhoea (IBS-D) predominant; $\bar{X} \pm SD$; *$p < 0.05$*

Rycina 1. *Wydalanie siarczanu 6-hydroksymelatoniny (6-HMS) z moczem u pacjentów z zespołem jelita nadwrażliwego w postaci zaparciowej (IBS-C) i biegunkowej (IBS-D); $\bar{x} \pm SD$; *$p < 0,01$*

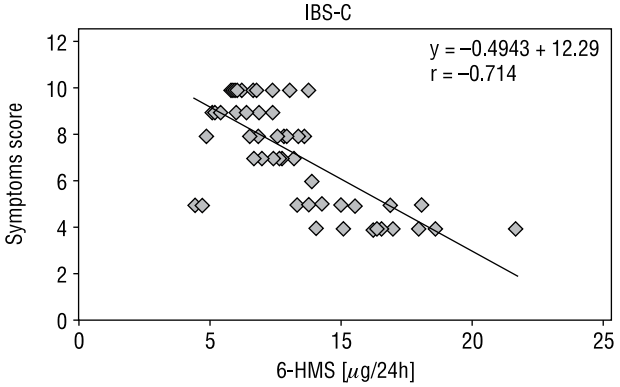

Figure 2. *Correlation between values of clinical index (symptoms score) and urinary excretion 6-sulfatoxymelatonin (6-HMS) in patients with irritable bowel syndrome with constipation (IBS-C) predominant*

Rycina 2. *Korelacja między wskaźnikiem nasilenia objawów a wydalaniem siarczanu 6-hydroksymelatoniny (6-HMS) z moczem u pacjentów z zaparciową postacią zespołu jelita nadwrażliwego (IBS-C)*

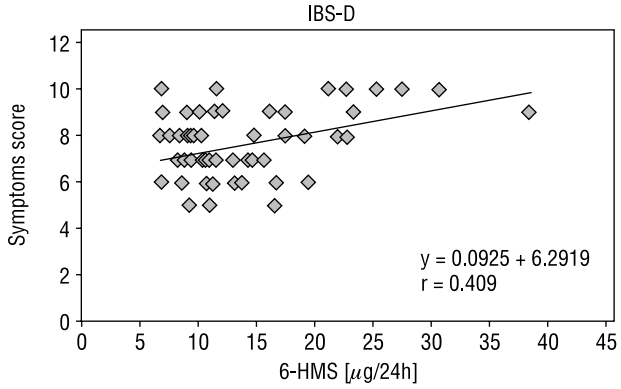

Figure 3. *Correlation between values of clinical index (symptoms score) and urinary excretion 6-sulfatoxymelatonin (6-HMS) in patients with irritable bowel syndrome with diarrhoea (IBS-D) predominant*

Rycina 3. *Korelacja między wskaźnikiem nasilenia objawów a wydalaniem siarczanu 6-hydroksymelatoniny (6-HMS) z moczem u pacjentów z biegunkową postacią zespołu jelita nadwrażliwego (IBS-D)*

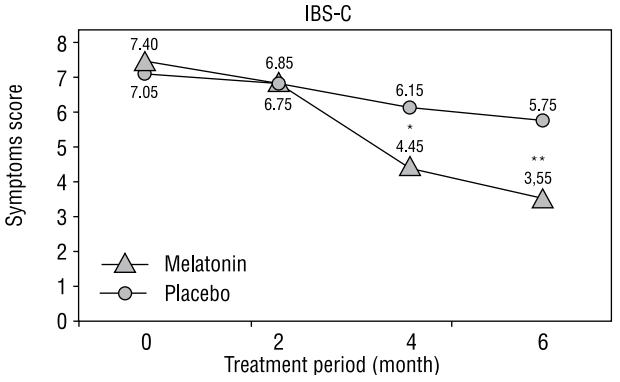

Figure 4. *Comparison of treatment results after placebo and melatonin administration in irritable bowel syndrome patients with constipation (IBS-C) predominant; *$p < 0.05$; **$p < 0.01$*

Rycina 4. *Wyniki leczenia melatoniną postaci zaparciowej zespołu jelita nadwrażliwego w porównaniu z placebo; *$p < 0.05$; **$p < 0.01$*

coefficient (r) was (minus) –0.714 (Fig. 2). In patients with IBS-D on the urinary this correlation was positive: r = 0.409 (Fig. 3).

In constipation-predominant IBS, melatonin decreased IBS symptoms more distinctly compared to placebo $\chi^2 = 29.901$ and $\chi^2 = 56.798$, respectively. These differences were statistically significant when evaluated in the four and six months of melatonin administration (Fig. 4). After six months, total regression of abdominal pain was observed in 12 patients (60%). At the same time, abdominal bloating decreased in 14 (70%) patients. Less favourable results concerned constipation because only in one person was the full effect noted, while in nine there was an improvement in bowel movement.

In diarrhoea-predominant IBS, a nine-week administration of melatonin did not change significantly the clinical picture of the disease and the results were similar as in the group with placebo $\chi^2 = 24.412$ and $\chi^2 = 25.739$ respectively (Fig. 5).

Melatonin was well tolerated. Only two women from the IBS-C group felt slight symptoms of fatigue in the morning hours and one slight vertigo in the first week of the therapy.

Discussion

The obtained results confirm the opinions of many researchers as to the beneficial effect of melatonin on the gastrointestinal tract, and the possibilities of

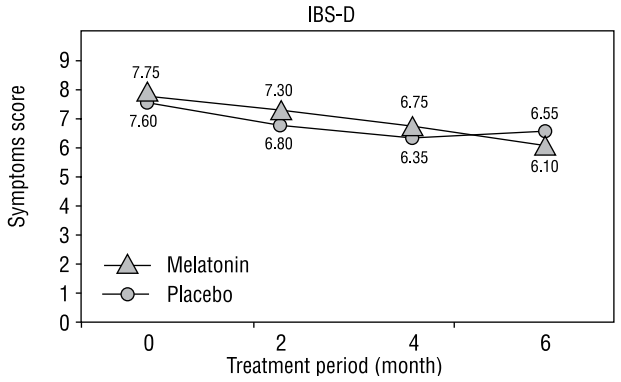

Figure 5. *Comparison of treatment results after placebo and melatonin administration in irritable bowel syndrome patients with diarrhoea (IBS-D) predominant; no statistical significance*

Rycina 5. *Wyniki leczenia melatoniną postaci biegunkowej zespołu jelita nadwrażliwego w porównaniu z placebo; brak znamienności statystycznej*

its use in the treatment of chronic diseases of this tract [26, 27].

Nevertheless, the effects of the treatment can vary and they can depend on the grade of its physiological secretion. The use of melatonin can be particularly justified in the case of its deficit in an organism [28]. Low secretion of melatonin at night has been found, among others, in oesophageal reflux disease [29], in functional dyspepsia and in duodenal ulcer disease [30, 31].

These changes should be related to individually differentiated secretion of pineal melatonin. However, in the case of intestinal diseases, the amount of secreted melatonin depends on other factors, mainly local ones. The number of EC cells can be such a factor as they proliferate in intestinal diseases. The results of studies to date have pointed to a changeable number of EC cells also in patients with IBS [32]. Spiller et al. [33] found an increased number of these cells in subjects with diarrhoea-predominant IBS. In turn, El-Sahly et al. [34] observed a decreased number of EC cells in constipation-predominant IBS.

In earlier studies, we demonstrated that secretion of melatonin in postmenopausal women is significantly decreased, but its metabolism in the liver is not disturbed [35].

A negative correlation between 6-HMS excretion and intensification of ailments from the GI tract is an important observation. The lowest excretion of this metabolite was found in women with persistent abdominal pain and sleep disorders. This may prove that melatonin deficit is one of the important factors of pathogenetic psychoemotional disorders in postmenopausal women.

The time and the cause-effect dependence between the secretion of melatonin and sex hormones is a different issue. It is known that melatonin secretion is associated with the organism aging. It can indirectly affect gonadal activity via gonadoliberin and gonadotropins secretion [36]. The direct effect cannot be excluded either. Higher melatonin concentration in the ovarian vesicles fluid suggests that this hormone may also be synthesised in gonads [37]. These suggestions are supported by studies confirming the presence of precursor compounds (tryptophan, serotonin) as well as enzymes engaged in melatonin synthesis — serotonin N — acetyl-transferase and hydroxyindole-O-methyl transferase, in the human ovary homogenates [38]. The effect of melatonin on both synthesis and secretion of sex hormones by ovarian vesicles is not unequivocally established. Some authors have described its inhibitory action on progesterone secretion [39], while others have observed a stimulatory effect [40]. Most recent authors think that melatonin does not show any significant impact on oestradiol secretion. Moreover, Okatani et al. [41] observed a negative correlation between oestradiol and melatonin in premenopausal women. They also showed that oestradiol administration in postmenopausal women reduced nocturnal increase of melatonin secretion. Luboshitzky et al. [42] observed that oestrogen treatment in women with hyperandregonaemia reduces usually elevated 6-HMS concentration in urine.

It is supposed that the association between oestrogens and melatonin is not exclusively based on the feed-back mechanism, but is more complex, with the tropic hormones playing the role in this process.

Irrespective of the above pathogenetic associations, the results of our studies have demonstrated marked melatonin deficit in some postmenopausal women. This justifies the usefulness of melatonin administration in a combined therapy of disorders associated with this period, particularly with the existing GI tract ailments after thorough analysis of the nature of these complaints. Mean urinary excretion of 6-HMS in women with IBS-C did not differ significantly from healthy subjects, whereas it was higher in IBS-D patients; this is opposite to the observation of Radwan et al. [23]. These differences may be dependent on various agents such as the number of enterochromafin cells and its activity, diets used during the period of examination, gender and age of patients, level of emotional disorders and others [43, 44]. The results of the treatment were more beneficial in IBS-C patients. Thus, it can be supposed that the beneficial effect was associated with melatonin's relaxative properties on the smooth muscles of the gut, which in consequence led to diminished abdominal distension. However, a positive melatonin effect on the psychoemotional sphere cannot be excluded because in this group of patients the placebo effect was also significant. Poor effect was obtained in the regulation of the rhythm of bowel movements both in the IBS-C

and the IBS-D group. Similarly, other researchers did not observe distinct changes in bowel movement in IBS subjects after 30 days of 3 mg/daily of melatonin administration [22]. To optimise the treatment it would be desirable to establish melatonin dose and the time of its administration. Most doctors recommend an evening dose of 3 mg so as not to disturb the circadian rhythm of endogenic melatonin release. Due to melatonin's short half-life (30−60 min.) it is justified to administer it in divided doses twice a day [45]. Patients with IBS have disturbances of the gastrointestinal tract (abdominal pain, bloating, diarrhoea) during the day, but never at night. For this reason, a fasting dose of melatonin may have a beneficial influence on GIT function. Moreover, melatonin is mainly catabolised to 6-HMS which also manifests biological activity, particularly antioxidant, and its appropriate level can diminish some adverse processes in the GI tract.

Therefore it appears that in selected cases recommendation of morning doses of melatonin is justified. Administration of melatonin in a combined treatment of IBS is also justified, but mainly in constipation-predominant IBS. The role of inflammatory factors is more frequently indicated [46, 47]. The anti-inflammatory effect of melatonin is not sufficient in these cases, but the possibility of the use of this hormone in the combined treatment of IBS is not excluded.

Conclusions

Melatonin can be used in the combined treatment of IBS, particularly in patients with constipation-predominant IBS.

Acknowledgement

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