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INFLUENCE OF TIANEPTINE ON MELATONIN HOMEOSTASIS AND PSYCHOSOMATIC SYMPTOMS IN PATIENTS WITH IRRITABLE BOWEL SYNDROME

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Selective serotonin reuptake inhibitors (SSRIs) exert beneficial effect on gastrointestinal tract (GIT), but its mechanism has not been recognized. One of the hypothesis assumes, that fluoxetine increases indirectly melatonin production. For this reason it can be hypothesized, that administration of drugs of opposite effect, for example tianeptine (selective serotonin reuptake enhancer (SSRE), can reduce melatonin production resulting in harmful effects as regards GIT. The aim of the study was to confirm or reject this hypothesis. The study included 100 patients, aged 21–58 years, with irritable bowel syndrome (IBS). Basing on the Rome III Criteria patients with constipation-predominant (IBS-C, n=50) and with diarrhoea-predominant (IBS-D, n=50) and 25 health volunteers (control group C) were distinguished. Visual Analog Scale (VAS) and Hamilton Depression Rating Scale (HDRS) were used to determine the severity of somatic and psychic symptoms. The concentration of 6-sulfatoxymelatonin (6-HMS) in the urine was measured by ELISA method. In both groups the patients were administrated tianeptine 12.5 mg three times daily or placebo for 8 weeks. After 8 weeks of tianeptine therapy no significant changes were found in urinary 6-HMS excretion both in IBS-C group (9.9±3.2 versus 11.5±3.5 µg/24 h) and in IBS-D group (11.8±3.3 versus 12.2±3.5 µg/24 h). Eight-week tianeptine therapy resulted in significant decrease of somatic and psychic symptoms in both investigated groups. The improvement in the quality of life indices was obtained in 76.5% of IBS-C and in 63.3% of IBS-D patients. Conclusions: tianeptine does not impair melatonin homeostasis in patients with IB, diminishes IBS symptoms and improves the patients' quality of life.

Key words: 6-sulfatoxymelatonin, irritable bowel syndrome, psychosomatic symptoms, tianeptine, melatonin

INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most common functional disorders of the gastrointestinal tract (1, 2). Its pathogenesis is complex, but brain-gut axis dysregulation is its main factor (3-7). Somatic symptoms are often accompanied by psycho-emotional disorders such as anxiety, low mood and even depression (8). Due to these reasons psychoactive drugs are used in complex treatment of IBS (9-11). These drugs can regulate intestinal motor activity and reduce visceral hypersensitivity (12, 13). Numerous drugs of different pharmacological properties are currently available. Although they are effective and generally safe, the choice of particular medication is not easy. The decision should be based on the knowledge of the mechanism of its action. It should be checked whether the patient understands the nature of his disease and whether he is able to accept taking medication for a few months.

Tricyclic antidepressants (TCAs) are applied in the treatment of IBS, particularly in patients in whom diarrhoea and abdominal pain are dominating symptoms and who weakly respond to spasmolytic drugs (14-16). These drugs show central analgesic effects and slow intestinal transit through an anticholinergic mechanism (17). Numerous side

effects of TCAs limit their use. Thus, safer and better tolerated medications, modulating the function of serotonergic system - selective serotonin reuptake inhibitors (SSRIs) are used in the treatment of mental disorders. However, there is no evidence confirming beneficial effect of SSRIs in IBS therapy because there are scarce experiments related to this problem (18-20). It is not known which properties of these drugs can have an advantageous effect. Generally, it has been assumed that with the inhibition of serotonin reuptake, its concentration in tissues increases, which through activation of 5-HT₃ and 5-HT₄ receptors releases the prokinetic effect. Thus, the application of SSRIs is justified in the cases of constipation predominant IBS (21).

It results from own experience that the prokinetic effect and the increase in stool frequency are observed mainly within the first two weeks of the treatment and not in all the patients. Moreover, other authors have not confirmed the influence of fluoxetine, the main representative of SSRIs, on visceral pain perception (22, 23). However, in experimental studies fluoxetine caused relaxation of intestinal smooth muscles (24). Thus, it seems that the mechanisms of the beneficial effect of fluoxetine on GI tract have not been recognized. One of the hypotheses assumes that fluoxetine increases indirectly

melatonin production by increasing the serotonin concentration in tissues and blood (25). Serotonin is the precursor of melatonin. Both neuromodulators are secreted in large amounts in the GI tract by enterochromaffin cells (26). Melatonin displays wide range of properties and wide spectrum of action, including antioxidant (27), enteroprotective (28), anti-inflammatory (29) and spasmolytic (30-35). It also affects mental sphere and is applied in the treatment of sleep disorders and its analogs (agomelatine) in depression therapy (36, 37). All these properties are used successfully in the treatment of IBS (38-41). Serotonin is a substrate for melatonin synthesis. Changes in serotonin catabolism caused by SSRI or SSRE play a key role in melatonin homeostasis, especially for subjects permanently managed with. Understanding of the way and intensity of these changes has cognitive and practical value. Assuming "melatonin" mechanism of SSRIs action, it can be supposed that administration of medication of opposite effect, as tianeptine, that means selective serotonin reuptake enhancers (SSREs), can reduce melatonin production resulting in disadvantageous effects as regards GI tract. This hypothesis requires either confirmation or rejection because drugs from this group are more commonly used in the medical practice of physicians of different specialty.

The aim of the study was to assess the effect of tianeptine on urinary 6-HMS excretion and on the somatic and psychic symptoms in patients with irritable bowel syndrome.

MATERIAL AND METHODS

Patients

All the patients received thorough information concerning the study and they signed the written consent prior to any actions. The study was also approved by the Ethics Committee of the Medical University of Lodz (RNN 238/05/KB).

The study included 100 patients, aged 21-58 years, with irritable bowel syndrome (IBS) and 25 healthy volunteers, aged 23-55 years (control group C). Basing on the Rome III Criteria patients with constipation-predominant (IBS-C; group I, n=50) and with diarrhoea-predominant (IBS-D; group II; n=50) were distinguished. The criteria of inclusion comprised the duration of

symptoms, minimum 12 months and no permanent improvement after spasmolytic, prokinetic and anti-diarrhoea therapy. The severity of main somatic symptoms (visceral pain, abdominal bloating, stool frequency) was estimated with Visual Analog Scale (VAS; 1-10 points). The mental state of the patients was also evaluated. Hamilton Depression Rating Scale was used to determine the severity of depression with the following scoring: 0-7 - no depression; 8-12 - mild; 13-17 - moderate; 18-29 - severe; >30 - very severe. Only patients with mild depression were qualified for the study.

In all the subjects enrolled in the study, the endoscopy examinations of the upper and lower part of the gastrointestinal tract were performed, histopathology of the colon mucosa was obtained, abdominal ultrasound was performed as well as the laboratory tests: the blood cell count, CRP, glucose, electrolytes, bilirubin, urea, creatinine, cholesterol, triglycerides, thyrosine and activity of the following enzymes: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGTP), alkaline phosphatase (ALP), amylase and lipase.

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

Seven days prior the evaluations all the medications were withdrawn and the same diet was recommended in all the patients, 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 red light in the hours from 9.00 p.m. till 7.00 a.m. and the same liquid diet was administered (Nutridrinks, Nutricia) in the amount of 3×400 ml of the caloric value - 1800 kcal and 1500 ml of the isotonic still water. At the same time the 24-hour urine collection was performed. Urine was kept at +4°C. Immediately after the end of 24-hour urine 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 ELISA method applying IBL antibodies (RE-54031, Immunological Laboratories) and Expert 99 MicroWin 2000 reader (Biogenet). The obtained results were converted from $\mu\text{g/ml}$ to $\mu\text{g}/24$ h.

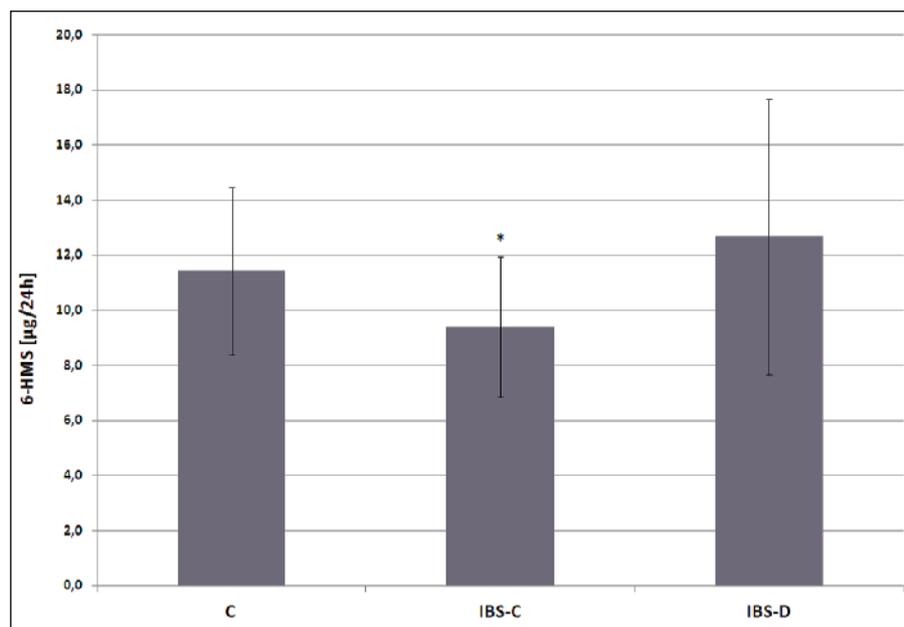


Fig. 1. The mean value of urinary 6-sulfatoxymelatonin (6-HMS) excretion in healthy subjects (C; n=25; 11.4 ± 3.0 $\mu\text{g}/24$ h) and patients with constipation predominant irritable bowel syndrome (IBS-C; n=50; 9.4 ± 2.5 $\mu\text{g}/24$ h) and with diarrhoea - predominant irritable bowel syndrome (IBS-D; n=50; 12.7 ± 5.0 $\mu\text{g}/24$ h); * $p < 0.05$.

Study design and procedures

After screening procedures the patients were randomly allotted into groups of 25 subjects each (subgroup a and b). In both groups the patients were administrated tianeptine (12.5 mg) or placebo three times a day after meals for 8 weeks. The severity of somatic and psychic IBS symptoms was estimated before and after the treatment.

Moreover, global IBS symptoms withdrawal, drug tolerance and adverse effects were assessed with the use of own questionnaires and the quality of life with modified IQOLASF-36v2-Polish 2004 questionnaire. After 8 weeks procedure with tianeptine was confirmed until 6 months and followed by next 6 months.

Statistical analysis

The data are presented as mean value \pm S.D. Categorical variables were compared with Chi-square test. Continuous

variable were compared with Student's t-test (between tianeptine and placebo group) with the paired t-test (baseline versus 8 weeks treatment in each group) and a multivariate analysis. All statistical analysis was performed using STATISTICA v. 9.0 package.

RESULTS

Twenty four-hour urinary 6-hydroxymelatonin sulfate (6-HMS) excretion in healthy subjects was 11.4 ± 3.0 $\mu\text{g}/24$ h (Fig. 1). In the group of IBS-D patients it was similar - 12.7 ± 5.0 $\mu\text{g}/24$ h ($p > 0.05$). However, in the group of IBS-C patients the excretion of this metabolite was significantly lower -9.4 ± 2.5 $\mu\text{g}/24$ h ($p < 0.05$).

After 8 weeks of tianeptine therapy no significant changes were found in urinary 6-HMS excretion both in IBS-C group (9.9 ± 3.2 versus 11.5 ± 3.5 $\mu\text{g}/24$ h) (Fig. 2) and in IBS-D group (11.8 ± 3.3 versus 12.2 ± 3.5 $\mu\text{g}/24$ h). No significant changes were noted after placebo administration (Fig. 3).

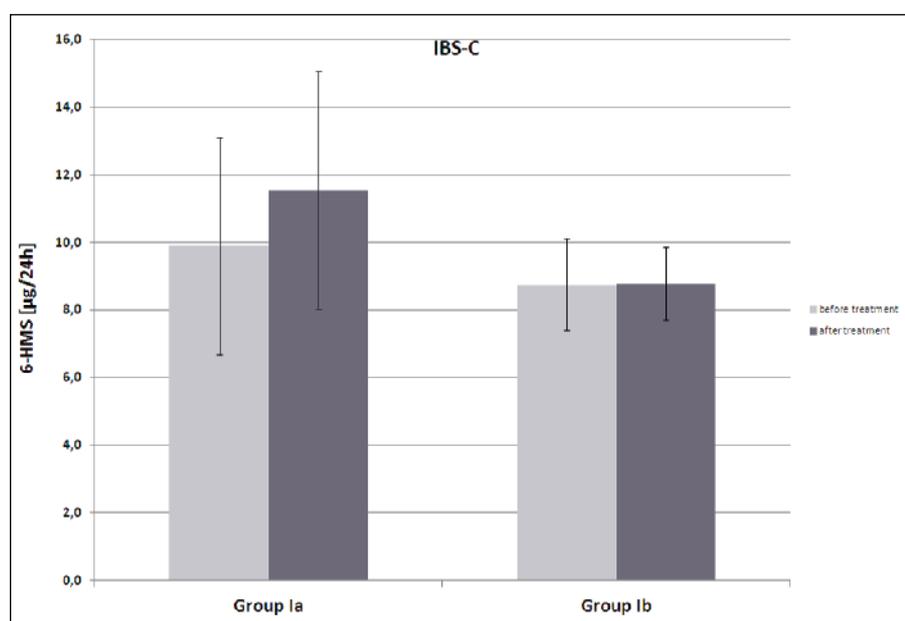


Fig. 2. The mean value of urinary 6-sulfatoxymelatonin (6-HMS) excretion in patients with constipation - predominant irritable bowel syndrome (IBS-C) before and after tianeptine (Group Ia; $n=25$; 9.4 ± 3.2 and 11.5 ± 3.5 $\mu\text{g}/24$ h) versus before and after placebo administration (Group Ib; $n=25$; 8.7 ± 1.4 and 8.8 ± 1.1 $\mu\text{g}/24$ h); there are no significant differences.

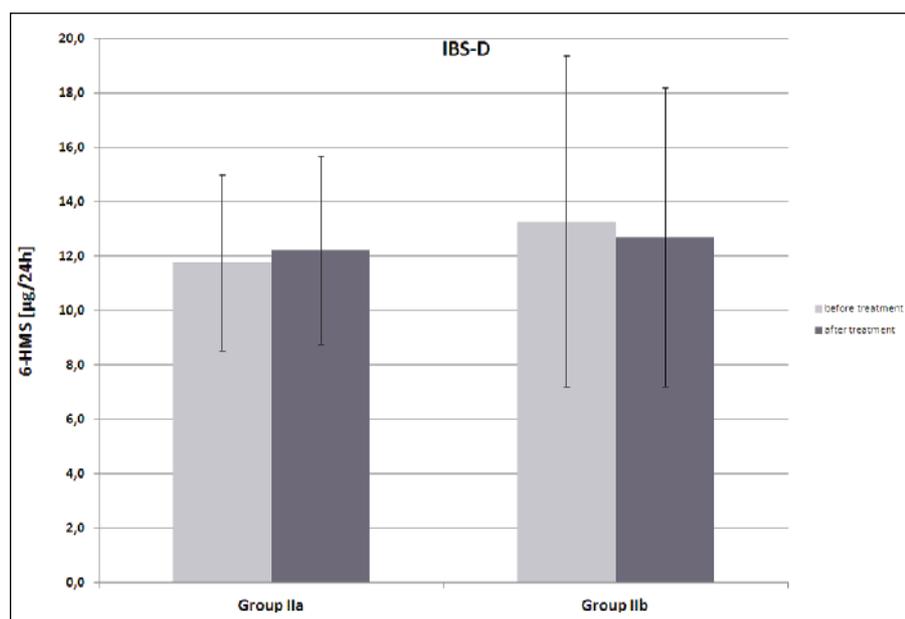


Fig. 3. The mean value of urinary 6-sulfatoxymelatonin (6-HMS) excretion in patients with diarrhoea - predominant irritable bowel syndrome (IBS-D) before and after tianeptine (Group IIa; $n=25$; 11.8 ± 3.3 and 12.2 ± 3.5 $\mu\text{g}/24$ h) versus before and after placebo administration (Group IIb; $n=25$; 13.3 ± 6.1 and 12.7 ± 5.5 $\mu\text{g}/24$ h); there are no significant differences.

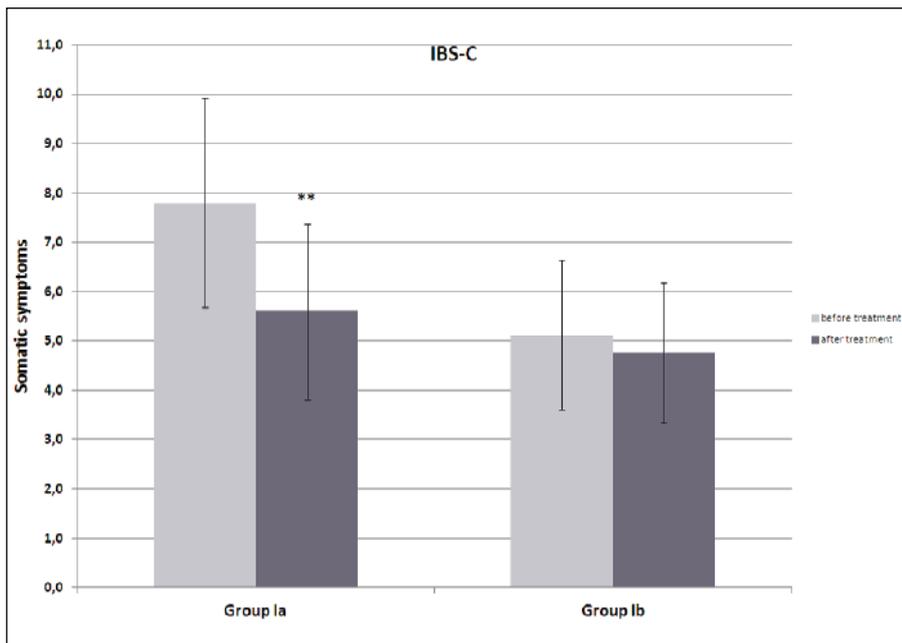


Fig. 4. Improvement of somatic symptoms in patients with constipation - predominant irritable bowel syndrome (IBS-C) before and after tianeptine (Group Ia; n=25; 7.8±2.1 and 5.6±1.8) versus before and after placebo administration (Group Ib; n=25; 5.1±1.5 and 4.8±1.4); ** p<0.01.

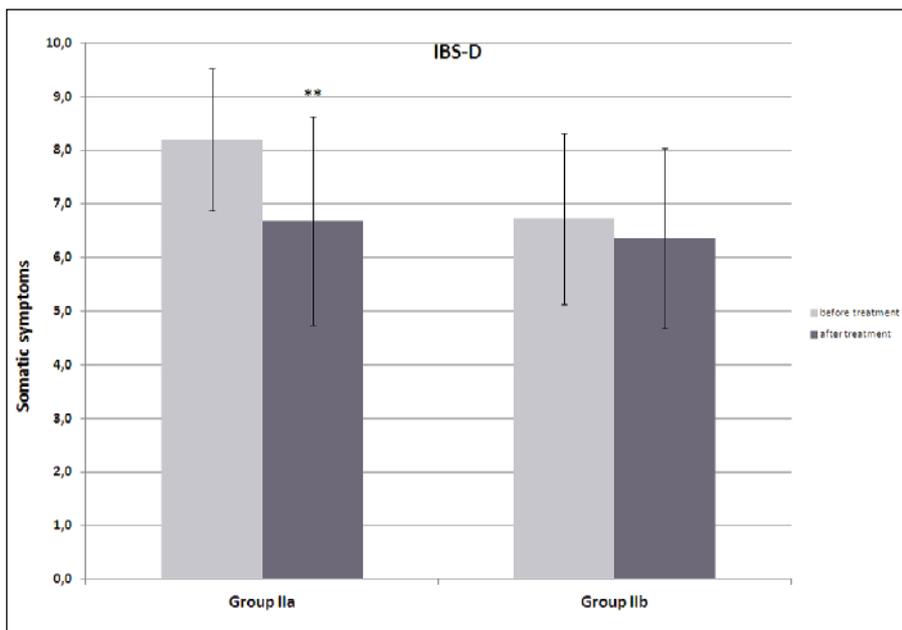


Fig. 5. Improvement of somatic symptoms in patients with diarrhoea - predominant irritable bowel syndrome (IBS-D) before and after tianeptine (Group IIa; n=25; 8.2±1.3 and 6.7±2.0) versus before and after placebo administration (Group IIb; n=25; 6.7±1.6 and 6.4±1.7); there are no significant differences.

Table 1. Mean values (mean ±S.D.) of biological parameters in subjects enrolled in the study.

ALP - alkaline phosphatase; ALT - alanine aminotransferase; AST - aspartate aminotransferase; CRP - C-reactive protein; GFR - glomerular filtration rate; GGTP - gamma-glutamyltransferase.

	Healthy subjects n= 25		IBS-C n= 50		IBS-D n= 50	
Age [years]	34.1±9.3		36.9±11.4		37.0±12.6	
Sex (F,M)	F=14	M=11	F=31	M=19	F=29	M=21
Albumin [g/dl]	5.5±0.6		5.4±0.3		5.2±0.4	
ALP [u/L]	36.9±9.2		34.6±7.0		37.8±10.1	
ALT [u/L]	23.3±7.2		21.4±6.5		24.6±7.0	
AST [u/L]	21.5±4.9		20.6±3.8		23.0±5.1	
Bilirubin [mg/dl]	0.7 ±0.3		0.7±0.2		0.9±0.3	
CRP [mg/dl]	1.1±0.4		0.9±0.6		1.6±1.1	
GFR [ml/min]	109.2±10.1		112.4±11.0		116.0±12.6	
GGTP [u/L]	25.4±6.3		26.8±5.4		27.1±4.8	
Hemoglobin [g/dl]	13.4±0.6		13.6±0.5		13.1±0.8	

Eight-week tianeptine therapy resulted in significant decrease of somatic symptoms in both investigated groups. The index of symptoms decreased in the group of IBS-C patients from 7.8 ± 2.1 to 5.6 ± 1.8 ($p < 0.01$) (Fig. 4), whereas in IBS-D group from 8.2 ± 1.3 to 6.7 ± 2.0 ($p < 0.01$) (Fig. 5). Compared to placebo, tianeptine improves abdominal symptoms effectively in both groups: IBS-C $\chi^2 = 6.096$ ($p < 0.01$); IBS-D $\chi^2 = 4.023$ ($p < 0.05$). Similarly we noted improvement of psychic symptoms index in the IBS-C patients from 9.4 ± 3.2 to 7.3 ± 2.7 ($p < 0.05$) and in IBS-D group from 8.9 ± 3.0 to 7.6 ± 2.3 ($p > 0.05$).

Most of the patients (82.6%) admitted that tianeptine therapy was beneficial; similar opinion was presented only by 23.8% patients using placebo; these differences are statistically significant ($p < 0.001$).

The improvement in the quality of life indices was obtained in 76.5% of IBS-C and in 63.3% of IBS-D patients. The quality of life deteriorated after placebo in these groups, respectively, in 21.6% and 16.9% of patients ($p < 0.001$). In general, tianeptine was well tolerated and adverse effects of low intensity appeared in 16 of 50 treated patients (26.6%). Headaches and dizziness were reported by 6 patients after 2 weeks of the therapy, oral dryness by 5, feeling of excessive fatigue by 3 and sleep disorders by 2 patients.

Generally, it can be stated that tianeptine does not interfere with melatonin secretion and metabolism in IBS patients. It has a beneficial effect on the clinical picture of this syndrome. It decreases both, psychoemotional and somatic symptoms, and improves the patients' quality of life.

DISCUSSION

Tianeptine is used mainly as antidepressant and its efficacy is comparable with that of SSRIs (42-46). Its main mechanism of action lies in the stimulation of serotonin reuptake by, among others, neurons and blood platelets and probably also by enterocytes (14); it does not affect noradrenaline and dopamine reuptake nor serotonergic, noradrenergic, dopaminergic or cholinergic receptors (47). However, it was found to decrease significantly blood serotonin level with simultaneous increase of blood dopamine and platelet serotonin concentration (48). Tianeptine elicits inhibitory effect on the function of hypothalamic-pituitary-adrenal axis that controls reactions to stress (49-51). This medication has no effect on vital physiological parameters such as pulse, arterial blood pressure or body weight (52). It does not interact with other drugs and its discontinuation is not associated with the onset of symptoms of abstinence (44, 53). All this encourages the use of tianeptine in psychosomatic diseases. In our earlier studies tianeptine was demonstrated to elicit beneficial effect on the somatic state of patients with ulcerative colitis (54, 55). Sohn *et al.* (56), in randomized, multicenter studies including 228 patients with diarrhoea-predominant IBS, proved similar therapeutic efficacy of tianeptine as compared to amitriptyline.

Reduction of symptoms such as abdominal pain and stool frequency the authors associated with the drop in serotonin level. In the presented our study positive treatment results were obtained both in constipation- and diarrhoea-predominant IBS. This result may be associated with anxiety-relieving and antidepressive effect but it does not exclude the role of melatonin in this process. It is important to note that tianeptine (despite the fears and theoretical assumptions) did not decrease melatonin production in any of the patient groups. Relatively high values of 24-hour urinary 6-hydroxymelatonin sulphate excretion prove that. This parameter is recognized to be a universal exponent of melatonin secretion and metabolism in an organism (57, 58). Thus, enhanced serotonin reuptake does not

affect significantly melatonin production. Most probably secretion of this indoleamine is conditioned by the number of enterochromaffin cells and expression of enzymes taking part in this synthesis (59).

Bolton *et al.* (60) investigated the effect of tianeptine on gastrointestinal motility of isolated rat stomach and colon. They found out that tianeptine inhibited contractions of both organs and this activity was not diminished by SSRI and NSRI group drugs. Relaxing effect of tianeptine might be associated with the increased blood level of dopamine and decreased blood level of serotonin (61). Serotonin enhances acetylcholine release via 5HT3 and 5HT4 receptors which causes smooth muscles contractions; tianeptine prevents that and this property has been used in the treatment of asthma (62). Cytoprotective effect of tianeptine was demonstrated in experimental studies with the use of indomethacin (62). Tianeptine, enhancing serotonin reuptake, can decrease its concentration in colonic wall and in consequence decrease motor activity.

Good tolerability is an essential feature of tianeptine. In our studies, adverse effects of low intensity were observed in some patients but only during two weeks period of initial treatment. They were mild and did not force to the discontinuation of the therapy. The number and kind of adverse effects induced by TCAs are significantly higher and some of them are very serious *e.g.* arrhythmia, hypotension, cholestatic jaundice, extrapyramidal signs and others (11). SSRIs are safer but they also can induce depression, insomnia, dyspeptic signs, tremor and the like. It results from this comparison that tianeptine is not only an effective but also safe medication for patients.

Summerizing, it should be emphasized that antidepressive medications can be useful in combined therapy of many gastrointestinal diseases because they alleviate both mental and somatic symptoms. Scepticism still existing among gastroenterologists as regards their use can result from lack of sufficient knowledge about the group of medications being continuously enriched in new pharmaceuticals. Tianeptine belongs to atypical antidepressive drugs and its pharmacological properties have not been recognized sufficiently so far. The results of own studies confirm the opinion of other researchers about multidirectional and beneficial effect of tianeptine in IBS.

Conclusions

1. Tianeptine does not impair melatonin homeostasis in patients with IBS.
2. Tianeptine diminishes IBS symptoms and improves the patients' quality of life.

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