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CLINICAL RESEARCH

Effect of 5-HT$_1$ agonist (sumatriptan) on anorectal function in irritable bowel syndrome patients

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Abstract

AIM: To evaluate the effect of sumatriptan, a selective 5-HT$_1$ agonist, on anorectal function in irritable bowel syndrome (IBS) patients.

METHODS: Twenty-two IBS patients selected according to the Rome II criteria (F 15, M 7; mean age 29.3±6.8, range 22-44 years) were examined. The study was blind, randomized and placebo-controlled with a crossover design. Anorectal manometry and rectal balloon distension test were performed before and after the administration of placebo and sumatriptan.

RESULTS: The administration of sumatriptan caused a significant increase in the resting anal canal pressure from 9.2±2.0 kPa to 13.1±3.3 kPa (P<0.0001) connected with the increase in the anal sphincter length and high pressure zone. After sumatriptan injection a remarkable increase in the threshold for the first sensation from 27±9 mL to 34±12 mL (P<0.05) and urge sensation from 61±19 mL to 68±18 mL (P<0.01) was observed. Sumatriptan did not affect either the volume evoking the rectoanal inhibitory reflex or the results of the straining test.

CONCLUSION: 5-HT$_1$ receptors participate in the regulation of anorectal function. Elucidation of the role of 5-HT$_1$ receptors in the pathophysiological mechanisms of IBS may have some therapeutic implications.

Key words: Sumatriptan; 5-HT receptors; Irritable bowel syndrome, Anorectal function

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INTRODUCTION

Serotonin (5-hydroxytryptamine, 5-HT) is one of the main neurotransmitters involved in the control of the gastrointestinal tract function and plays an important role in the pathophysiology of irritable bowel syndrome (IBS)[1,2]. A number of abnormal motor and sensory patterns reported in IBS patients is supposed to be a result of disturbances in serotonergic mechanisms. Different 5-HT receptor subtypes are involved in the regulation of enteric reflexes and signaling to the central nervous system[3]. Pharmacological data confirm that the specific 5-HT$_3$ antagonists and 5-HT$_4$ agonists are beneficial in the management of IBS[4-6]. Among new emerging serotonergic agents for functional gastrointestinal disorders the role of 5-HT$_1$ agonists was discussed[7]. Many IBS patients complain of various non-gastrointestinal symptoms and disorders such as headache, migraine, non-cardiac chest pain, back pain, dysuria, sleeping difficulties, chronic fatigue syndrome, fibromyalgia syndrome, anxiety and depression. From the clinical point of view frequent coexistence of IBS with headache reported by 23%-45% of IBS patients may also indicate the common pathogenetic and therapeutic link for these diseases, possibly related to the serotonin-dependent processes[8].

Sumatriptan is a selective 5-HT$_{1B/D}$ agonist used for migraine treatment. Recent research results on sumatriptan effects on the gastrointestinal tract function have shown that the drug alters oesophageal motility, favours transient lower oesophageal sphincter relaxations despite the increase in the lower oesophageal sphincter pressure, prolongs postprandial fundic relaxation delaying gastric emptying, and induces a premature intestinal third phase of the migrating motor complex in the jejunum. Encouraging results have been obtained in patients with dyspepsia and impaired postprandial gastric relaxation treated with sumatriptan[9,10]. A therapeutic potential for 5-HT$_1$ agonists in IBS patients has been also suggested according to the observation that sumatriptan causes a significant relaxation of the descending colon influencing the perception of colonic distension.

Anorectal function in IBS draws attention due to commonly reported symptoms by patients with this disorder including urgency, excessive straining or feeling of incomplete evacuation. Up to now, consistent association

between the above symptoms and anorectal dysfunction has not been clearly established. In some IBS patients anorectal manometry is performed to exclude abnormalities that may coexist with or imitate IBS. Moreover, assessment of anorectal function in IBS patients, particularly by use of anorectal manometry, presents an easily accessible way to evaluate the effects of drugs on the lower gastrointestinal tract function[11].

The aim of the present study was to test the hypothesis that sumatriptan influences anorectal function in patients with IBS.

MATERIALS AND METHODS

Subjects

Twenty-two IBS patients selected according to the Rome II criteria (15 women (F), 7 men (M); mean age 29.3± 6.8, range 22-44 years) participated in the study. Based on the bowel pattern, three subgroups of IBS patients were distinguished – constipation predominant IBS (C-IBS: 5 F, 0 M), diarrhea predominant IBS (D-IBS: 3 F, 4 M), and alternating IBS (A-IBS: 7 F, 3 M).

The organic causes for the symptoms were excluded by the evaluation of detailed medical history and physical examination, basic laboratory tests and normal colonoscopy within the five years preceding inclusion in the study. Patients who previously underwent abdominal or gastrointestinal surgery, except for appendectomy, were not included. Patients with ischemic heart disease, arterial hypertension, after myocardial infarction or cerebral stroke, and over 45 years of age were not included in the study, either. Blood pressure and heart rate values in all subjects were within the normal range. All patients had a normal electrocardiogram performed just before the study. The study was approved by the Ethics Committee of the Medical University Hospital and written informed consent was obtained from all subjects.

Recording methods

Anorectal manometry and rectal balloon distension were performed using a four lumen water-perfused catheter with a polyethylene balloon attached to the tip (Zinetics Manometric Catheter, Medtronic). Pressure was sensed by external pressure transducer connected to an analogue-digital converter (PC Polygraph, Synectics Medical, Synecpol). The system was calibrated at 0 and 6.67 kPa at the beginning of each study. The following measurements were derived from the manomertic recordings: the maximal anal resting pressure (MRP) and the maximal anal squeeze pressure (MSP); the anal sphincter length (SL) and high pressure zone (HPZ) within the anal canal, both during rest and squeeze. Moreover, strain, squeeze and cough tests as well as volume initiating the internal anal sphincter relaxation (rectoanal inhibitory reflex, RAIR) and volume required to elicit first sensation, urgency and discomfort or pain were evaluated.

The maximal resting and squeeze pressure along the anal canal was measured from the rectum to the anal margin by the dynamic pull-through technique. The procedure was performed both in the normal relaxed state and in the voluntary squeeze state by pulling a catheter through the sphincters at a speed of 10 mm/s. Three pulls in both states were performed. Evaluation of the strain and cough tests were carried out using the stationary pull-through technique. RAIR and sensory thresholds were measured by the intermittent, phasic rectal distension, starting with 10 mL of air and increasing in steps of 10 mL. The rectal balloon was emptied after each distension. The duration of the distension amounted to 60 s, with 40-60 s intervals between each inflation. During distensions subjects were asked to report and classify their sensation in terms of the first sensation, urge sensation and the maximal tolerable volume due to discomfort or pain. Whenever unbearable discomfort or painful sensation were experienced during any level of distension the experiment was immediately suspended.

Study protocol

Patients examined after an overnight fast without a cleansing enema in the left lateral position were allowed to acclimate to the assembly for 20 min. Patients were instructed not to take any analgesic, spasmolytic, anxiolytic, antidepressant, or anti-inflammatory agents within 72 h before the examination. Women participating in the study were examined within the first part of the menstrual cycle. The study was blind, randomized and placebo-controlled with a crossover design, in which each subject received placebo and drug on two separate days at least one week apart. After the baseline recordings sumatriptan 6 mg sc (Imigran, Glaxo Wellcome Group) or saline 0.5 mL sc was given in a random fashion. The second recordings were performed 30 min after the administration of the drug or placebo. Therefore, four recordings in each subject were performed (recording before and after sumatriptan injection, and recording before and after placebo injection). Blood pressure and heart rate were monitored during the study. All adverse events were noted.

Pressure data converted by PC polygraph were displayed, recorded, and analyzed on an IBM-compatible computer using Polygram software (Synectics Medical). Baselines were automatically set by the computer program. The amplitude was measured from the baseline to the peak of the resting and squeeze pressure area. The maximal resting anal pressure and the maximal squeeze anal pressure were defined as the mean of the three highest values observed at any site in the anal canal during three pulls in the relaxed state, and in the squeeze state, respectively. Each increase in the pressure during pull was later marked as an event in the tracing. The position of the event marked the position of the anal sphincter. The anal sphincter length is a product of the applied catheter pulling speed and time of the pressure increase during the pull-through procedure. The length of the zone with a pressure higher than the half of the maximal anal resting pressure value was defined as the high pressure zone.

The cough reflex was evaluated by measuring the mean of the three highest increments in the anal canal pressure during cough. The anal canal pressure during attempts to defecate was evaluated to assess the presence of pelvic floor dysynergia. RAIR was defined as a 20% reduction or more in the resting anal pressure in response to the rectal distension. The perception corresponding to each distend-

Table 1 Effect of sumatriptan on manometric and volumetric anorectal parameters in IBS patients (mean ± SD)

Anorectal parameter	Placebo	Sumatriptan
Maximal resting pressure	9.2±2.0 kPa	13.1±3.3 kPa[b]
Sphincter length during rest	4.0±0.5 cm	4.5±0.4 cm[b]
High pressure zone during rest	2.6±0.3 cm	3.1±0.5 cm[b]
Sphincter length during squeeze	5.1±0.4 cm	5.4±0.5 cm[b]
Urge sensation threshold	61±19 mL	68±18 mL[b]
First sensation threshold	27±9 mL	34±12 mL[c]
High pressure zone during squeeze	2.8±0.6 cm	3.0±0.7 cm[c]
Pain threshold: ≤100mL/>100mL (number of patients)	13/9	8/14
Rectoanal inhibitory reflex (RAIR)	21±8 mL	21±9 mL
Straining test results:		
Proper relaxation/lack of relaxation/ contraction (number of patients)	14/7/1	13/8/1
Maximal squeeze pressure	25.5±8.5 kPa	27.2±8.4 kPa
Maximal cough pressure/maximal resting pressure	2.9±0.8	3.1±1.1

[b]P<0.01, [c]P<0.05, *vs* Placebo.

Paired Student's t test was used in all cases except for analysis of straining test results and pain thresholds where chi-square test was used.

ing volume up to 100 mL was recorded.

Statistical analysis

Data are expressed as mean±SD unless otherwise stated. Statistical analysis was performed using paired Student's t test and the chi-square test, as well as EPIINFO statistical package ver. 3.2. Differences were taken to be significant for values of P<0.05.

RESULTS

Influence of placebo on anorectal function

The effect of placebo on the anal sphincter function and rectal perception thresholds was assessed in all 22 IBS patients participating in the study. Administration of placebo had no significant influence on the manometric parameters or on visceral perception thresholds. No changes in the distending volumes inducing the first rectal perception, urgency or pain sensations were observed. Lowered pain threshold (distending volume ⩽ 100 mL), considered as a sign of visceral hypersensitivity in IBS patients, was reported before and after the placebo administration in 12 and 13 patients (55% and 59%), respectively.

Effect of sumatriptan on the anal sphincter function

As compared with placebo, sumatriptan considerably increased the maximal resting pressure (MRP) from 9.2±2.0 kPa to 13.1±3.3 kPa (P<0.0001). The rise in the maximal squeeze pressure (MSP) was not statistically significant (P=0.0634, Table 1). After sumatriptan injection the increase in the anal canal pressure in response to cough (maximal cough pressure, MCP) was higher than after placebo injection. However, the increase in the MCP was proportional to the corresponding resting pressure, as the ratio MCP/MRP after the drug injection was not altered (P=0.245, Table 1). Manometric evaluation of the anal canal pressure during attempts to defecate revealed improper response in 9 patients (41%). Signs of pelvic floor dyssynergia appeared as paradoxical contractions of the anal sphincters in one subject and as a failure to relax the pelvic floor in 8 patients. The administration of the drug, as in the placebo case, did not change the results of the straining test. The anal sphincter length as well as high pressure zone of sphincter pressure evaluated by the pull-through technique during both rest and squeeze remarkably increased after sumatriptan injection (Table 1).

In comparison of the volume evoking the rectoanal inhibitory reflex (RAIR) after placebo and sumatriptan administration, which were respectively 21±8 mL and 21±9 mL, no significant difference was shown (P=0.665).

Effect of sumatriptan on visceral perception

According to the conscious rectal sensitivity thresholds, 30 min after sumatriptan injection significant increases in the thresholds for the first sensation from 27±9 mL to 34±12 mL (P< 0.05) and urgency from 61±19 mL to 68±18 mL (P< 0.01) were observed. During the baseline recordings lowered rectal pain sensation evoked with the distending volume up to 100 mL was observed in 13 IBS patients (59%) including 5 out of 7 D-IBS patients, 8 out of 10 A-IBS patients, and none of C-IBS patients. After the administration of the drug rectal pain threshold increased in 5 out of 13 patients, but in 8 (36%) it was still evoked by the distending volume up to 100 mL. The increase in the pain threshold was not significant (P=0.227).

Adverse events

After placebo administration in 5 out of 22 patients (23%) transient burning sensation in the place of injection was reported. No other adverse events were observed, except for one patient who complained of mild but long-lasting headache (about 7 d). A variety of side effects after the drug administration was reported in 20 out the 22 patients enrolled (91%). The majority of the adverse events were mild to moderate in severity. They began at a mean of 4 min (range 2-8 min) after sumatriptan injection and lasted for a mean of 12.5 min (range 1-25 min). The most commonly reported adverse events after sumatriptan injection were: burning sensation in the place of injection in 45% of patients; headache and throat tightness in 36%; weakness in 32%; tingling of lower and upper jaw or temple and formication of the head or face skin in 27%; flare in the place of injection, heaviness in chest, limbs, and in head in 23%; nose tightness, dyspnoea, bodily warmth, acroparesthesia, abdominal pain or discomfort in 9%; and nausea, drowsiness as well as total numbness in 4.5%. Many side effects occurred simultaneously, but the typical triad of symptoms, called "triptan sensations", i.e. throat tightness, heaviness in chest and bodily warmth, was not observed in any patient. In two patients after sumatriptan administration short-lasting proctalgia (about 1 min) occurred.

DISCUSSION

Based on the manometric evaluation, anorectal dysfunction in IBS patients included the signs of pelvic floor dysynergia observed in 41% of patients and lowered visceral pain thresholds in 59% of patients, particularly in

those with diarhoea predominant IBS and with alternating bowel pattern. According to the literature data an obstructive pattern of defecation is exhibited in about 20% of healthy subjects. Two times higher prevalence of improper response to the straining test in IBS patients, whether constipated or not, may suggest general changes in pelvic floor mobility in IBS. The presented results have shown that sumatriptan, a selective 5-HT$_{1B/D}$ agonist, noticeably affects anorectal function in IBS patients.

The drug administration in a standard therapeutic dose of 6 mg sc induces a considerable increase in the maximal anal resting pressure, and much less significant increase in the maximal anal squeeze pressure. The increase in the anal canal resting pressure observed after sumatriptan administration reflects mainly the internal anal sphincter contraction. On the contrary, squeeze pressure depends mostly on the external anal sphincter. Similarly, other manometric parameters characterising anorectal function and being connected with the anal canal pressure, such as the functional sphincter length and high pressure zone, increased as well. The maximal cough pressure after the drug injection was proportional to the corresponding resting pressure. Sumatriptan did not have any impact on the straining test results.

Interestingly, sumatriptan has also revealed its influence on visceral sensation thresholds. The increases in the first sensation and urge sensation thresholds were proved to be statistically important. During evaluation of rectal sensation, lowered pain threshold with the distending volume up to 100 mL was evoked in 59% IBS patients, which is in accordance with the literature data[12]. Visceral hypersensitivity was common in D-IBS and A-IBS, but not in C-IBS. After sumatriptan administration a tendency to lower visceral hypersensitivity in IBS patients was observed. The statistical analysis, however, did not confirm the significance of the increase in the pain threshold probably due to methodological limitations as with the maximal distending volume amounting to 100 mL not in all IBS patients pain or discomfort sensation was evoked. To evaluate precisely the influence of sumatriptan on rectal pain threshold another study would be needed, in which higher distending volumes and optimally a barostat or tensostat would be used. Regarding the results of the recent studies which have shown that sumatriptan affects the discomfort threshold during gastric and colonic distension, similar observation may be expected in the rectum. The influence of sumatriptan on colonic motility is important for further evaluation.

For better understanding of the role of 5-HT$_1$ receptors, the effect of sumatriptan on lower gastrointestinal tract function in the different subgroups of IBS patients as well as in healthy subjects should be investigated. From the methodological point of view, a crossover design of the study enabled us to avoid considerable interindividual variability common in functional testing such as anorectal manometry. However, an intraindividual variability could still have some impact on the manometric and volumetric parameters. Foster and colleagues used a similar protocol of the study evaluating the effect of sumatriptan on the oesophageal motility. All the women participating in the study were investigated in the follicular phase, as it has been shown that the menstrual cycle affects rectal sensitivity in IBS patients but not healthy volunteers[13]. Patients were examined after an overnight fast to eliminate the gastrointestinal reflexes and the postprandial increase in visceral sensitivity[14,15].

The majority of the adverse events were mild to moderate in severity and short-lasting. However, it cannot be totally excluded that they might stress the patients, and in this way affect the results to some extent.

Several recent studies dealt with the effect of sumatriptan on the upper part of the gastrointestinal tract[9]. Two observations were particularly important from the clinical point of view. The first one concerned chest symptoms, which occurred in 3-5% of patients using sumatriptan in the migraine treatment. Foster *et al* in the study on 16 healthy subjects have shown that a therapeutic dose of sumatriptan (6 mg, sc) altered oesophageal motility without affecting the ECG, supporting at the same time an oesophageal rather than cardiac cause for the sumatriptan-induced chest pain. However, contrary to what happened in healthy subjects, the drug failed to modify either the wave's amplitude or lower oesophageal sphincter tone in patients with ineffective oesophageal motility[16]. The second important observation having a potential therapeutic implication concerned the influence of sumatriptan on gastric fundic tone and sensitivity to distension[9]. Tack and co-workers[9] have shown that in some dyspeptic patients sumatriptan is able to restore impaired gastric accommodation to a meal and improve the early satiety symptom. A therapeutic potential for 5-HT$_1$ receptor agonist is suggested not only in functional dyspepsia, but in other functional gastrointestinal disorders, in particular IBS. The preliminary observation has revealed that sumatriptan causes a significant relaxation of the descending colon influencing the perception of colonic distension.

The present study has confirmed that sumatriptan affects not only the upper but also the lower part of the gastrointestinal tract, including anorectal function and rectal sensation thresholds. The sumatriptan-induced decrease in rectal sensitivity may have a therapeutic implication in IBS patients, particularly in patients with visceral hypersensitivity.

The effect of sumatriptan on the anal sphincter function should be also considered in patients using this drug in the form of suppository. In two patients after sumatriptan injection a short-lasting, transient proctalgia occurred. Hypothetically, it could result from the increase in the maximal resting pressure, or even spasm of the anal sphincter. However, no clinical observations have confirmed this hypothesis so far. On the other hand, various forms of the drug may differently affect gastrointestinal function. For example, it has been shown that, unlike the subcutaneous formulation, the intranasal administration of sumatriptan has no significant effect on gastric sensory and motor function, probably due to a low bioavailability of intranasally administered sumatriptan[17].

Since the resting anal canal pressure depends essentially on the internal anal sphincter (IAS) function the increase in its value after sumatriptan administration seems to result mainly from the IAS contraction. Up to now, research on neurological and pharmacological control of the IAS

function has evaluated quite precisely the role of the adrenergic and cholinergic systems. Recently, the role of non-adrenergic non-cholinergic (NANC) system involving nitric oxide (NO) as a neurotransmitter has been also investigated. Anorectal manometry and rectal sensitivity testing proved to be a useful method for evaluating the influence of pharmacological agents including serotonergic drugs acting on anorectal function in IBS patients[11]. It has been shown that serotonin induces contraction of the IAS, while ketanserin (a 5-HT_2 receptor antagonist) and cisapride (a 5-HT_4 receptor agonist and partial 5-HT_3 receptor antagonist) evokes the IAS relaxation in healthy subjects[18,19]. Prucalopride, a novel selective 5-HT_4 receptor agonist, seems not to influence the anorectal function either in IBS patients or in healthy controls[20], whereas tegaserod, the next 5-HT_4 receptor agonist, decreases sensitivity to rectal distension in healthy subjects[21]. In the study of Thumshirn *et al*[22] alosetron, a 5-HT_3 receptor antagonist, has no significant effect on gastrointestinal transit or rectal sensory and motor mechanisms in patients with non-constipated IBS. Interesting results have been obtained by Siproudhis *et al*[23] who investigated effects of two types of serotonergic antidepressants, amitriptyline and fluoxetine, on anorectal motility and visceral perception. Both antidepressants similarly relaxed the IAS, probably through a non-specific mechanism, without modifying visceral perception. Only amitriptyline relaxed the external anal sphincter[23].

The mechanisms underlying the sumatriptan-induced anorectal function changes remain unclear. The distribution of various types of 5-HT_1 receptors and particularly their role in the gastrointestinal function are also poorly identified. Anorectal function, and in particular visceral perception, are modulated at different levels of the brain-gut axis and theoretically, sumatriptan could be acting at each of these levels[24]. Potential mechanism for the effect of sumatriptan on anorectal function could occur via activation of the 5-$HT_{1B/D}$ receptors acting on enteric neurons. Alternatively, sumatriptan could be acting on sensory nerve terminals to modulate neurotransmitter release. A further possible mechanism could involve a central action of sumatriptan. However, pre-clinical data indicate that sumatriptan only poorly penetrates the blood-brain barrier making a central mechanism less probable.

A nitrergic pathway as a possible mechanism of the drug action on the gastrointestinal function has also been discussed. It has been already shown that the sumatriptan-induced relaxation of gastric fundus is partially mediated through the activation of an NANC mechanism, involving NO as a neurotransmitter, and the sumatriptan-induced relaxation of the gastric fundus is reversibly blocked by inhibition of NO synthase. However, regarding the fact that NO is the main neurotransmitter involved in the occurrence of RAIR, the lack of sumatriptan effect on the volume evoking RAIR might argue against the nitrergic mechanism. More likely a direct smooth muscle response may be modified. Sumatriptan induces not only the anal sphincter contraction, but as it has been shown in another study it causes also the increase in the lower oesophageal sphincter pressure.

Furthermore, it has been already shown that sumatriptan is able to induce endocrine secretion in men, and at the same time, for example somatostatin or glucacon can affect anorectal function. However, measurement of plasma somatostatin and glucagon concentration before and after administration of sumatriptan rules out their release as a mechanism by which sumatriptan may influence gastrointestinal function.

Sumatriptan may alter the perception of rectal distension due to its direct impact on the rectal tone. It has been already shown that the sumatriptan-induced gastric or colonic relaxations induce changes in visceral perception[9,10]. Likewise, higher volume thresholds during rectal sensitivity testing after sumatriptan administration may occur secondary to the drug-induced relaxation of the rectum. Therefore, further studies using a barostat or impedance planimetry are needed to explain this issue. The results obtained hitherto warrant further studies to clarify and verify the regulatory role of 5-HT_1 receptors in the gastrointestinal function and the mechanisms responsible for the effect of sumatriptan on the gastrointestinal sensorimotor function including receptor subtypes involved, and central *vs* peripheral mechanism. Selective and safe 5-HT_1 receptor ligands which are now lacking will be crucial for the future research.

In conclusion, the effect of sumatriptan on the anal sphincter function and rectal sensitivity thresholds indicates that 5-HT_1 receptors participate in the regulation of anorectal function. Better understanding of the role of these receptors in the pathogenesis of IBS may have some therapeutic implications, particularly in patients with visceral hypersensitivity. The possible application of anti-migraine drugs in the management of functional gastrointestinal disorders remains an open issue.

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