Migraine and Gallbladder Motility

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Abstract

Introduction Five (5) hydroxitryptamine (5-HT) selective receptor agonists (triptans) were reported to have gastric motor effects. However, less is known about their role on gallbladder (GB) motility.

Aim: Assessment of GB motility in patients treated with orodispersable triptans for migraine's attacks.

Patients and Methods: Out of 112 patients with various forms of migraine who required triptans while having headache attacks, followed-up in our ambulatory service, we have selected 30 patients diagnosed with mild to moderate migraine. These patients include: 15 with aura (3 men, 12 women, mean age=41,8±16,42 years) and 15 without aura (2 men, 13 women, mean age=47,73±18,50 years). Consequently, they had an ejection fraction (EF) of GB which is less than 60% (previously measured in intercritic period by elipsoid ultrasound Dodds method). Furthermore, no record of prokinetic or proton pump inhibitor treatments, gastric surgery, gallstones, collagen or thyroid disease, diabetes mellitus, cardiac, liver, kidney failure or cancer disease was recorded. The measurements of the GB were made while having a migraine attack, before and in every 15 minutes till 90 minutes. This was after receiving 5 mg of orodispersable zolmitriptan.

Results: There are no statistical significant difference between initially EF of the two groups (p=0,8190). Patients with migraine with aura showed a mean EF=42,53±4,31% before therapy. After therapy, the mean EF improved significantly: 48,80±3,23% (p=0,0001). Patients having migraine without aura displayed an initially mean EF=42,53±3,27%. In addition, they had a

very statistically significant response to therapy with important improvement of EF to 61,47±7,07% (p<0,0001).
Conclusions: 5HT selective receptor agonists increased GB motility, in migraine attacks with a response above the cut-off range of EF, in patients having migraine without aura.

Keywords: 5HT selective receptor agonists, migraine, GB motility

Introduction

Gastrointestinal (GI) motility is a complex process which includes different entities like: myoelectrical and contractile activity, compliance, tone, and movements known as gut transit. This complicated physiology of gut motility is under the supervision of local and circulating neurohumoral substances. However, one of them is hydroxitryptamine or serotonin (5-HT), which is an important neurohormonal transmitter. 5-HT is synthesized and stored mainly in two cell types: 90% in enterochromaphine (EC) cells and 10% in the neurons of the gut. Then, it is released into the blood in various situations like: postprandially, in case of local changes of the pressure across the gut wall, or as a response to specific stimuli (Bearcroft et al., 1998).

Therefore, it is believed that 5-HT is released into the gut wall from the store zones located at the basolateral aspects of EC cells and then spread into the lumen (Hansen, 1997).

A lot of investigations have been done in order to reveal the exact role of 5-HT in the regulation of gut motility. The difficulty of this attempt was consistently increased by the existence of many 5-HT receptor subtypes with various locations and effects. Hence, that is why the precise roles of 5-HT and 5-HT receptors are completely understood (Sarna et al., 2000).

It is now accepted that 5-HT selective receptor agonists (triptans) represents one of the most important modern therapy in migraine attacks, but some of their pathophysiology and clinical implications are still subject to discussions (Bigal et al., 2009).

5-HT selective receptor agonists were reported to have esophageal effects at the level of the lower sphincter and gastric motor effects. Thus, this is mainly during the process of accommodation. Moreover, less is known about their role on gallbladder (GB) motility (Houghton et al., 1992; Cipolla et al., 2001; Moroa, 2004; Deixler & Helmke, 2005).

Aim

The aim of this study is to assess GB motility response to orodispersable triptans in patients with migraine with or without aura, and previously known with impairment of the GB emptying.

Patients and Methods

In this study, 30 patients were diagnosed with migraine according to International Headache Society criteria (Olesen & Lipton, 1994). 15 with aura (3 men, 12 women, mean age=41,8±16,42 years) and 15 without aura (2 men, 13 women, mean age=47,73±18,50 years) were enrolled in this study. However, this was done after a thorough clinical examination and history taking. Biochemical blood tests such as blood smear, erytrocyte sedimentation rate (ESR), C reactive proteine (CRP), fasting sugar, alanin-transaminases (ALT), blood nitrogen urea and creatinin, sodium and potasium, level of thyroid stimulating hormone (TSH), urine biochemical and bacteriological tests, electrocardiogram (ECG), thoracic X ray, and cerebral CT scans were performed in order to rule out any possible associated conditions.

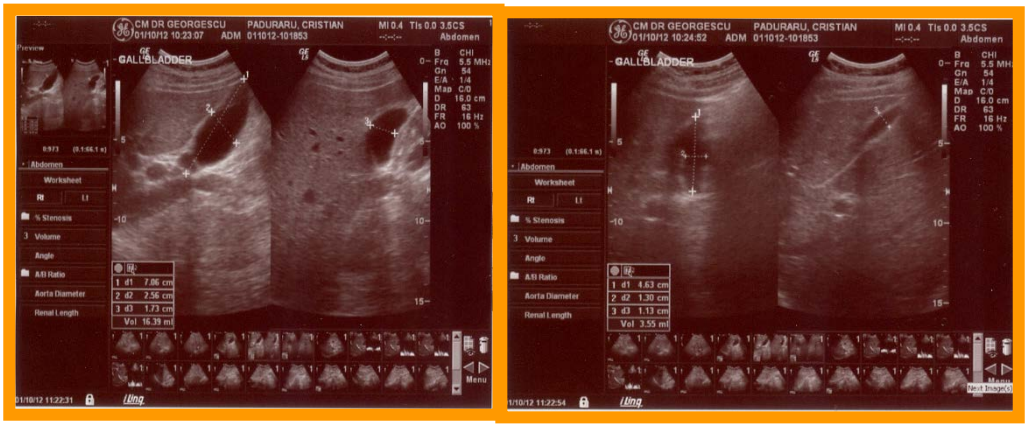
The severity of migraine attacks was set according to Migraine Disability Assessment (MIDAS) questionnaire (Stewart et al., 2001). Headache pain intensity was assessed by a 10 point pain scale (0 indicating no headache and 10 indicating severe headache). The MIDAS questionnaire was used to assess disability related to headache during daily activities (work, home and family commitments, leisure or social activities). The migraine disability was graded into four classes according to MIDAS scores: 0-5 as minimal, 8-10 as mild, 11-20 as moderate, and 21 or more as severe disability.

Measurements of GB motility were made using a cholecystokinetic meal consisting of 2 egg yolks (one egg yolk having about 55 calories, 4.5 grams of total fat and 1.6 grams of saturated fat, 210 mg of cholesterol, 8 mg of sodium, and 2.7 grams of protein) in 112 migraineurs and 15 healthy controls. From these patients, we have selected 30 patients having a decreasing of the GB emptying under the cut-off value of 60% of EF.

Biliary sonograms were obtained with a very high resolution ultrasound machine General Electric Logiq 7, with a multifrequency convex array probe (3,5-5,5 MHz). Measurements included transverse and longitudinal views of the GB, with clear anatomical relationship to the liver, kidney, and portal vein, for a positive identification. With the patient in the supine position, the probe was placed at the right upper quadrant. Once GB was identified, longitudinal oblique and transverse axial views were obtained. In addition, we measured the 3 dimensions of GB (depth, height, width). For volume (V), calculations was done using the ellipsoid formula: Volume (V) = $\pi/6 \times$ (width × height × depth) (Dodds et al., 1985). The mathematical formula is given as: EF = (initial volume-maximum residual volume/initial volume) × 100.

GB normal emptying ultrasound aspects in healthy controls, with normal EF above 60%, are depicted in figure 1.

Figure 1. Ultrasound aspects of GB motility in healthy controls



Ultrasound features of GB motility in patients, within intercritic periods with low EF, are illustrated in the figure below (Figure 2).

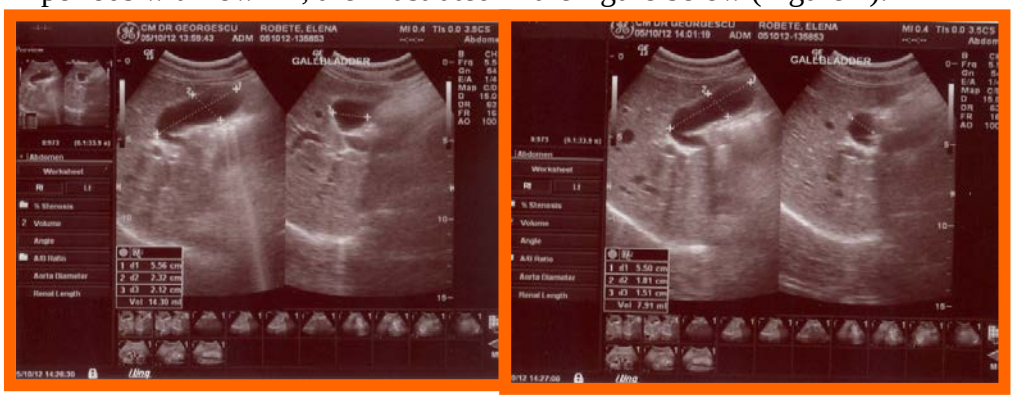


Figure 2. GB motility in patients within intercritic periods

The same measurements of GB were made while having a migraine attack. This was done before and at every 15 minutes till it gets to 90 minutes after receiving 5 mg of orodispersable zolmitriptan, with consecutive calculation of the EF.

Inclusion criteria include migraine with or without aura, intensity mild to moderate, treatment with 5-HT, and an ejection fraction (EF) of GB < 60%, which was previously measured using elipsoid ultrasound Dodds method.

Exclusion criteria include prokinetic or proton pump inhibitor treatments, previous gastric surgery with vagotomy, EF above 60%, gallstones, collagen or thyroid disease, diabetes mellitus, cardiac, liver or kidney failure, and cancer disease.

Furthermore, the study was approved by the local ethical committee. Also, both the patients and their families provided written informed consent.

Statistical analysis was made using GraphPad software with the panel for continuous data. This was done with the calculation of the mean values and standard deviation, unpaired t test, and p values with CI= 95%.

Results

As seen in the table below (table 1), there are no statistical significant differences between the two groups (migraine with aura versus migraine without aura) from a biochemical point of view. This was except for the body mass index (BMI) and sistolic blood pressure (BP), where p<0,0001.

Table 1. Clinical and biochemical baseline data

Parameters	Group 1	Group 2	P
Age (years)	41,8±16,42	47,73±18,50	0,36 (ns)
BMI (kg/m²)	31,93±2,49	26,46±1,75	<0,0001
Sistolic BP (mm Hg)	150,47±4,09	129,93±4,98	<0,0001
Hemoglobin (g%)	12,96±0,69	13,087±0,57	0,59 (ns)
Leukocytes (x10³/ml)	7,6±0,03	7,56±0,79	0,89 (ns)
Platelets (x10³/ml)	267,67±60,26	268,33±55,41	0,97 (ns)
ESR (mm/h)	12,57±2,74	13,73±3,73	0,35 (ns)
CRP (IU)	0,7±0,26	0,97±0,24	0,66 (ns)
ALT (IU)	28,53±4,72	29,93±6,81	0,53 (ns)
Fast blood sugar (mg%)	96,47±4,72	86,40±6,17	0,97 (ns)
TSH (IU)	4,03±0,78	4,00±0,66	0,92 (ns)
Nitrogen urea (mg%)	38,8±7,91	35,87±7,70	0,31 (ns)
Creatinin (mg%)	1,09±0,21	1,15±0,23	0,47 (ns)
Sodium (mval/ml)	141,87±4,76	140,07±4,18	0,28 (ns)
Potassium (mval/ml)	4,07±0,25	4,06±0,27	0,94 (ns)

Legend: ns= nonsignificant

Subsequently, the first group of patients, having migraine with aura, tends to display more elevated values of BMI and sistolic BP.

Some ultrasound features of the motility of GB, in a patient after receiving zolmitriptan, are illustrated in the figure below (Figure 3):

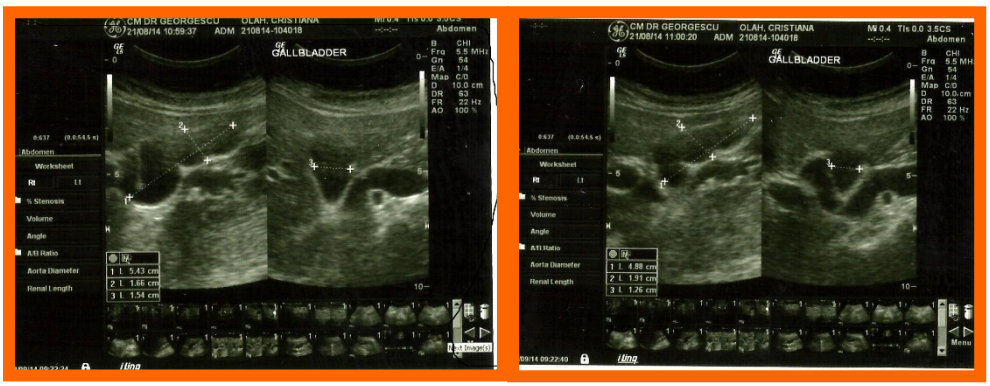


Figure 3. Maximal GB contraction after receiving zolmitriptan

There was no statistical significant difference between initially EF of the two groups (p=0,8190). As seen in figure 4, patients with migraine with aura (group 1) showed a mean EF=42,53±4,31% before therapy. After therapy, the mean EF improved significantly: 48,80±3,23% (p=0,0001).

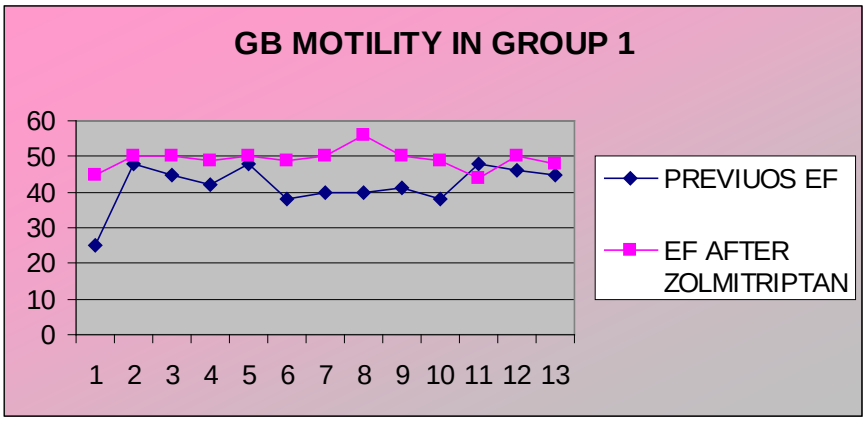


Figure 4. Motility of GB with EF in group 1 (with aura)

Patients with migraine without aura (group 2), displayed an initially mean EF=42,53±3,27%. Hence, they had a very statistically significant response to therapy with the increasing of EF up to 61,47±7,07% (p<0,0001, above the cut-off value of 60%).

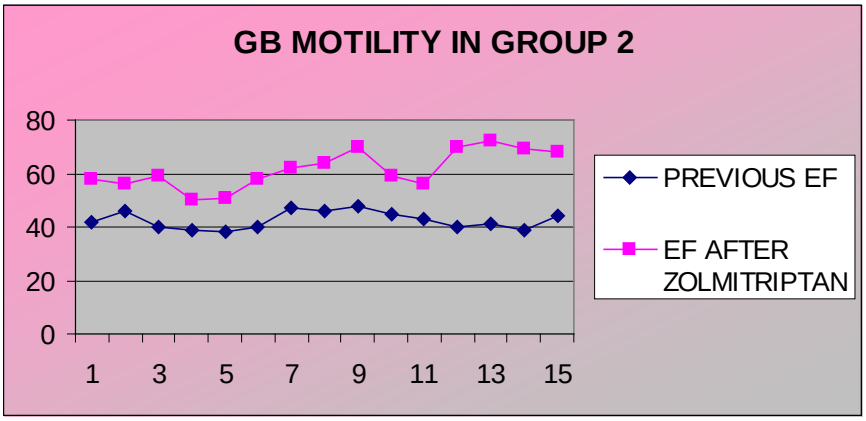


Figure 5. GB motility with EF in group 2 (without aura)

Discussions

Serotonin is a monoaminergic neurotransmitter with activities that modulate diverse central and peripheral functions. The central nervous system stores close to 2% of the body's serotonin. At this level, serotonin affects food intake, sleep, anxiety, sexual behavior, and mood. On the other hand, in the peripheral system where close to 98% of the body's serotonin is

synthesized and stored, serotonin operates as a peripheral hormone. This peripheral hormone affects vasoconstriction, intestinal motility, primary hemostasis, liver repair, and the control of the T cell-mediated immune system (Hansen, 2003).

A lot of study has been done with 5-HT 1, 2, 3,4, and 7 subtypes, in order to understand their role in the gut motility. Thus, it is now believed that subtype 1 of 5-HT stimulates the tone or motility of the lower esophageal sphincter and small intestine. It has an inhibitory effect over the tone or motility of the stomach, large intestine, and rectum. However, it seems that at some point, the multitude of 5-HT receptors, acting at the same level, may have similar or opposite actions e.g. either contraction or relaxation (Houghton et al., 1992; Borman and Burleigh, 1997; Coulie et al., 1999; Tack and Vanden Berghe, 2000).

The existence of a large variety of 5-HT receptors, makes the understanding of their various effects in different situations to be very difficult (Hixson, Lehrmann & Maickel, 1977).

In a mice model, in a Japanese study, the authors were able to demonstrate that injection with serotonin could result in a GB contraction, with the emptying of GB and the excretion of the bile (Hitoshi et al., 2010).

However, the working relation between exogenous administration of serotonin and production of cholecystokinin (CCK) at duodenal level is not clear. This is known a long time ago as a major key in the excretion of bile by the GB contraction (Ivy & Oldberg, 1928).

Based on this view, an interesting observation states the fact that most 5-HT receptors do not seem to affect normal function, acting only in disease conditions. An example can be seen in a 5-HT receptor antagonist, and alosetron which delays intestinal transit in irritable bowel syndrome diarrhea-predominant (IBS-D) patients, but not in healthy controls (Camilleri et al., 1999; De Ponti and Tonini, 2001).

Some 5-HT 1B/D agonists like sumatriptan may also alter esophageal motility, favoring a gastro-oesofageal reflux (Houghton et al., 1994). Another study showed the effect of Sumatriptan on the gastric motility in humans pointing the fact that 5-HT1B/D receptor agonists delay the stomach emptying (Coulie et al., 1997).

Zolmitriptan is a 5-HT selective agonist of the 1B/1D subtype receptors. Thus, according to our results, it improves the gallbladder motility. This is achieved by the stimulation of the GB emptying in migraine attacks and in patients that previously had a decreasing of the EF of GB.

Consequently, this effect seems to be more prominent in patients having migraine without aura, by which the administration of zolmitriptan could normalize the EF, by increasing it above the range of 60%.

By opposite, patients having migraine with aura, having also some minor associated metabolic issues like low grade obesity and higher blood pressure (nonmedicated), did not tend to have such a sustained response, resulting in an increasing of the EF but still below the cut-off range of 60%.

Whether or not zolmitriptan was orally administered in usual dosage, it should have an equal effect on GB contraction and emptying. This is irrespective of the severity or type of migraine that needs to be addressed in further discussions and investigations.

Conclusion

5-HT selective 1B/1D receptor agonists, administrated as orodispersable zolmitriptan, increased previously disturbed GB motility in migraine's attacks.

In patients with migraine without aura, we have observed a normalization of GB which empties with an increasing of EF in a range above the cut-off value of 60%.

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