UNDERSTANDING DYSPEPSIA IN PATIENTS WITH PARKINSON'S DISEASE

Georgescu Doina
Simu Mihaela
Lighezan Daniel
" Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania

Abstract

Objectives: Better understanding dyspepsia in Parkinson's disease (PD) in order to improve patients quality of life.

Methods: 27 patients (17 men,10 women, mean age=68,11± 12,62 years) diagnosed with PD (Hoehn-Yars scale), treated with levodopa or dopamine agonists, with gastrointestinal autonomic disorders and disturbances of gastric motility assessed by ultrasound approach undertook a trial consisting of a treatment with Trimebutine 300 mg/day for 3 months. We have assessed digestive severity symptoms scores before and after therapy: no symptoms=0, mild=1, medium=2, severe=3, comparing also to gastric motility curves.

Results: Before therapy 15 patients showed delayed of the gastric emptying (55,56%), 7 normal motility (25,92%) and 5 patients rapid emptying (18,51%).Symptoms severity scores before therapy were: 8 patients (29,52%) mild ,14 patients (51,85%) medium and 5 patients (18,51%).severe. Mean dyspepsia severity index in patients with gastric motility disorders before therapy was 2,20±0,52.After therapy the same index decreased to 1,50±0,69(p=0,0009).Gastric motility curves showed an improving after therapy more important in those with delaying emptying varying with 23,45%±14,03 versus 15%±5,87% in patients with rapid emptying (either p<0,001).

Conclusions An important range of patients with PD, with nausea and vomiting presented gastric motility disorders (74,07%), most of them having delay of the emptying and a satisfactory response to the treatment with Trimebutine with improving of symptom severity index and also gastric motility.

Keywords: Parkinson's disease, autonomic disorders, dyspepsia

Introduction

The autonomic problems of Parkinson's disease as non-motor features include gastrointestinal (GI) and urinary dysfunction, and a variety of other problems, such as sweating, sexual dysfunction, drooling that are in fact, other burden to deal with.

GI dysfunction is often seen, patients complaining of disturbances of intestinal habit with constipation, bloating, flatulence and abdominal pain. Some studies reported a high prevalence of constipation (58%) among patients with PD [Magerfurth 2005, Cersosimo 2008]. But many of dyspeptic symptoms are also related to troubles of the gastric motility probably due to neurodegenerative processes that also involved digestive system, specific dopaminergic medication and many other causes that are not yet fully understood. There are studies showing a prevalence of delaying of gastric emptying up to 70% of patients with PD [Ceravolo 2010].

Considering some similarities between FD and GI involvement in PD with autonomic disorders, we decided to manage the dyspeptic troubles of patients with PD with an agent used for his prokinetic abilities, like Trimebutine. Trimebutine acts on the gastrointestinal tract via (1) an agonist effect on peripheral mu, kappa and delta opiate receptors and (2) by releasing of gastrointestinal peptides such as motilin and modulation of the release of other peptides, including vasoactive intestinal peptide, gastrin and glucagon. Trimebutine accelerates gastric emptying, induces premature phase III of the migrating motor complex in the intestine and modulates the contractile activity of the colon[Hyama et all, 2007].

Patients and methods

Study design : open label clinical study in a cohort of 27 patients (17 men,10 women, mean age=68,11± 12,62 years), diagnosed with PD according to Hoehn-Yars scale [Ramaker, 2002].

Patients showed at enrolment associated non-motor GI dyspeptic symptoms like nausea, vomiting and bloating and the neurological disease was treated with levodopa or dopamine agonists at the Neurological Clinic, County Hospital Timisoara. Before joining this study they were also thoroughly gastroenterological evaluated. Lab tests and endoscopic digestive work-up were performed.We ruled out gastro-intestinal and gallbladder conditions, infection with Helicobacter Pylori, treatment with NSAID or aspirin. Diabetes mellitus, thyroid and collagen disorders, hepatic and renal failure were also criteria of unselection. Assessment of gastric motility was based on ultrasound approach with study of the emptying of the stomach [Bolondi,1985].Patients who showed disorders of the gastric emptying received Trimebutine. The study was aproved by the local ethical comitee and patients and their families provided written informed consent.

Ultrasound examination of the stomach with assessment of antral emptying was based on the measurement of antral area in a sagittal section of the gastric wall through the aortic and mesenteric artery plane. We calculated maximal antral distension (percentage of antral area distension after finishing the fluid-solid test meal), half time of gastric emptying (T½). Measurements were made from time 0 every 15 minutes until 90 minutes using a highly performance ultrasound device(General Electric Logiq 5 Expert, convex array transductor 3,5-5 Mhz).Ultrasound measurements were performed in patients and 10 controls (mean age=60,4±5,31 years) and gastric antral motility curves were drawn.

Patients received a treatment with Trimebutine 300 mg/day, for 3 months; no cases of drop out were recorded. After finishing the treatment we repeated the ultrasound examination of gastric motility. We have assessed digestive severity symptoms scores before and after therapy (no symptoms =0, mild=1, medium=2, severe=3) comparing also to gastric motility curves.

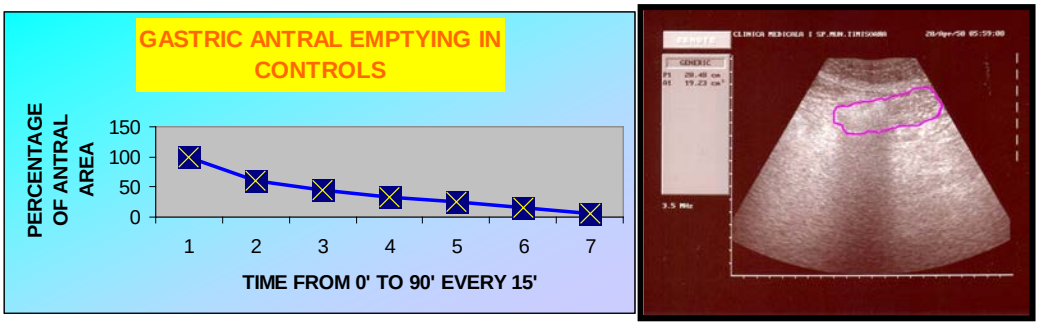

Figure 1. Antral motility in controls (mean values percentage T½) and ultrasound feature

Demographic patients chart showed that they lived in urban or proximity urban locations with very good access to medical attention.

Statistical analysis was made using GraphPad software with the panel for continous data, with descriptive statitistics and calculation of mean values and standard deviation, unpaired t test, statistical distribution and interpreting p values with CI= 95%, for setting the statistic significance and nonparametric Spearman correlation with calculation of r coefficient in order to quantify the magnitude and direction of correlation.

Results

Our patients baseline neurological data, as revealed in the figure below, showed that at the time of starting this study, they had various PD disease staging, according to Hoehn-Yars scale : with 1 point 1 patient (3,70%), with 1,5 points 1 patient (3,70%), with 2 points 7 patients (25,92%), with 2,5 points 1 patient (3,70%), with 3 points 14 patients

(51,85%), with 4 points 2 patients (7,40%), and with 5 points 1 patient (3,70%).

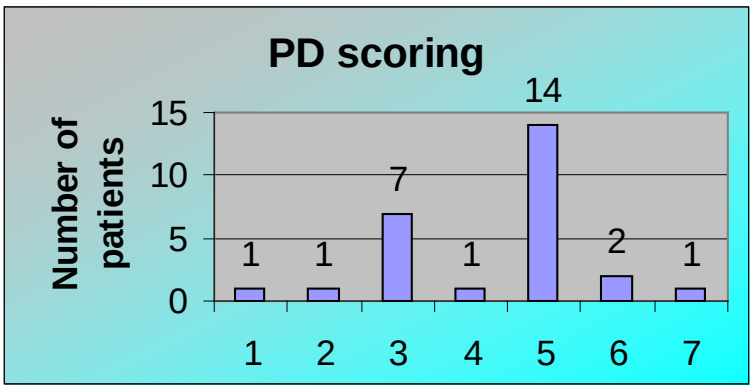

Figure 2. Staging of patients with PD at the start of the study

As depicted in the figure 3, before therapy, on ultrasound examination, the majority of patients (15 patients= 55,56%) showed delay of the gastric emptying, a quarter of patients (7 patients= 25,92%), displayed normal motility and a small percentage (5 patients = 18,51%), had a rapid gastric emptying.

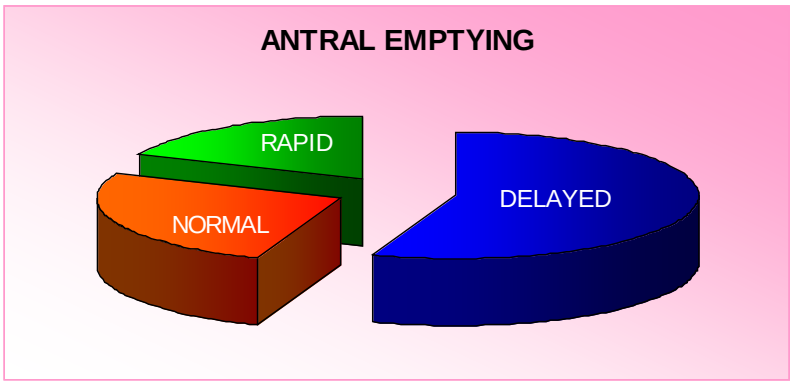

Figure 3. Ultrasound results of antral motility

Analysis of symptoms severity scores before therapy are shown in the figure below. In 8 patients (29,52%) we‘ve found mild symptoms, in 14 patients (51,85%) medium severity symptoms and in 5 patients (18,51%) severe complaints.

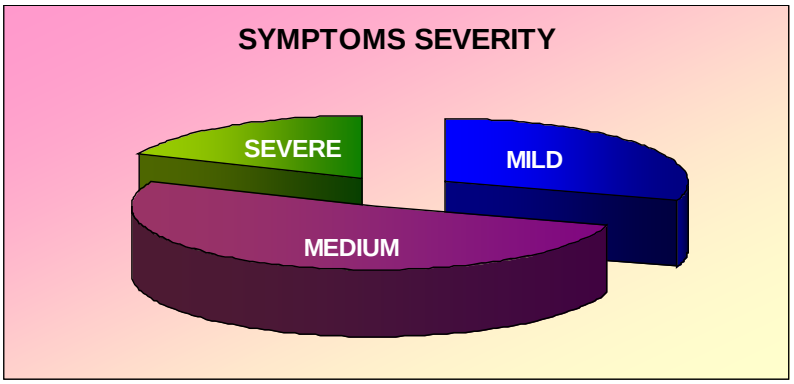

Figure 4. Symptoms severity

No significant correlation between severity scoring of PD and dyspepsia was set (r=0,081).

Table with dyspepsia and antral motility related to therapy

	BEFORE THERAPY	AFTER THERAPY	P
Mean dyspepsia index in patients with motility disorders	2,20±0,52.	1,50±0,69	p=0,0009
T½ antral percentage in patients with delaying emptying	24,45±14,039	44,05±11,95	P=0,0001
T½ antral percentage in patients with rapid emptying	68,83±3,82	55,80±3,19	P=0,0002

As shown in the table above mean dyspepsia severity index in patients with gastric motility disorders before therapy was 2,20±0,52. After therapy the same index decreased to 1,50±0,69, p=0,0009, being highly statistical significant.

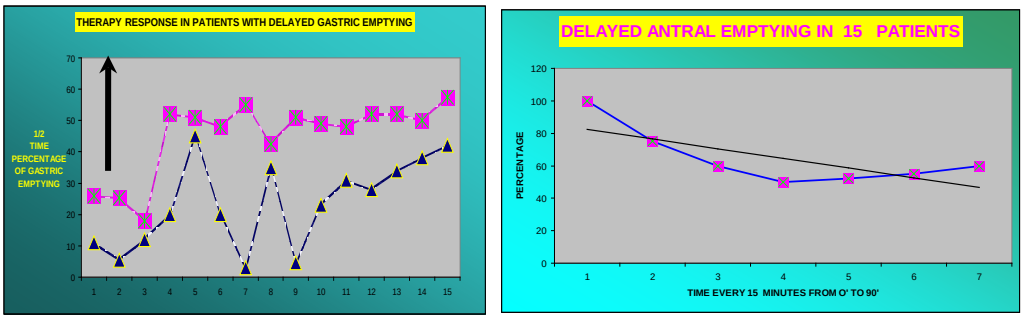

Figure 5. Delayed antral emptying and therapeutic respone

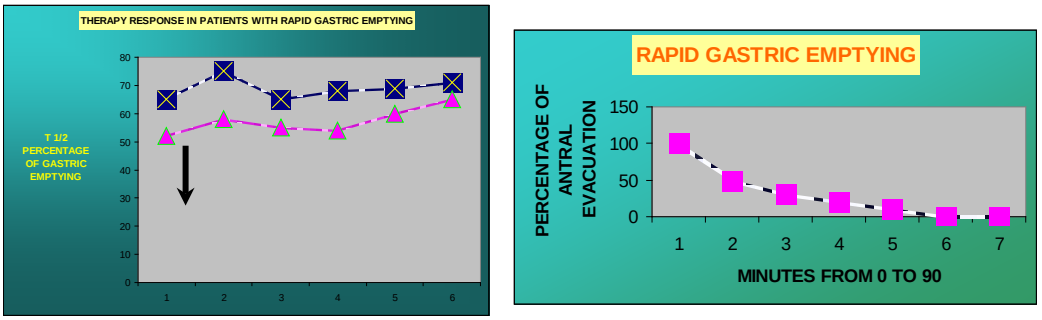

Figure 6. Rapid antral emptying and therapeutic response

Gastric motility curves showed an improvement after therapy with 23,45%±14,03% ($p<0,0001$) in those with delaying emptying; in patients with rapid emptying of the stomach we recorded an improvement with 15%±5,87% ($p<0,001$).

Discussions

Non-motor symptoms in patients with PD are very frequently reported from early stages of disease. In a two years followed-up study in patients with previously untreated PD, the incidence of non-motor complaints was very high. In fact nearly all patients (97,8%) reported at enrollment at least one symptom of a nonmotor issue[Erro at al, 2013].

There are studies that advocated the fact that:"pathology of Parkinson's disease (PD) extends far beyond the nigrostriatal system and results in non-motor symptoms coexisting with motor symptoms"[Rupam, 2010].

As stated above these non-motor symptoms are not related to the disease extent, by the contrary they are present quite early in the evolution of PD and sometimes even precede motor symptoms by years in patients that are practically not diagnosed with PD. It's quite clear that they cause significant morbidity and lower the quality of life in patients that are already suffering [Lim and Lang, 2010].

It was also reported that they are often under recognised by health professionals [Parsons et al. 2006].

The effect of various therapeutic modalities on non-motor symptoms is still unclear.There are some studies about correction of dysphagia and constipation showing different modalities of treatment[Cucci 2008, Parsons 2006, Tateno 2011, Rupam 2012]. However there is no recording data regarding gastric dismotility treatment with Trimebutine in PD.

Trimebutine is a therapeutic agent prescribed mostly in patients with functional dyspepsia(FD), irritable bowell syndrome, chronic constipation and other functional gastro-intestinal disorders due to its effect on the

regulation of the motility of the digestive system [Schmolson and Chang, 2011].

In a metaanalysis published in J Gastroenterology and Hepatology in 2007 it was clearly highlighted the significant treatment benefit in favor of prokinetic agents, including Trimebutine in patients with FD [Hyiama et al, 2007]. Other studies that analysed FD and its treatment also reported good results in treatment with prokinetic, Trimebutine being one of them [Schmolson and Chang, 2011].

From what we know this is the first study with Trimebutine in patients with PD and non-motor GI disorders. Our data after finishing the first session of treatment with Trimebutine showed a good toleration, with no report of side-effects or drop-out cases. The treatment response was satisfactory both in terms of gastric motility management and also in mitigating the dyspeptic syndrome.

However, there was a better outcome in patients with delaying of the gastric emptying, motility curves showing an improvement with 23,45%±14,03% vs. 15%±5,87% ($p<0,0001$ high significant), in those with rapid gastric emptying.

Further observation should be taken in order to see how much GI responsivity to this treatment will be maintained in a long term therapy.

Conclusion

An important range of patients with PD having dyspepsia exhibited at ultrasound examination gastric motility disorders (74,07%), most of them having delaying of the gastric emptying.

We recorded a satisfactory response to the treatment with Trimebutine, with improving of symptom severity index and gastric motility both ways, but better in patients with delaying of the gastric emptying.

References:

Bolondi L, Bortolotti M, Santi V, Calletti T, Gaiani S, Labò G. Measurement of gastric emptying time by real-time ultrasonography. Gastroenterology, 89(4):752-9. 1985

Ceravolo R., Rossi C., Kiferle L., Bonuccelli U.,Nonmotor Symptoms in Parkinson's Disease: The Dark Side of the Moon. Future Neurology. 5 (6): 851-871. 2010

Cersosimo MG, Benarroch EE: Neural control of the gastrointestinal tract: implications for Parkinson disease.Mov. Disord. 23, 1065–1075. 2008

Ciucci, M.R., Barkmeier-Kraemer, J.M. and Sherman, S.J. Subthalamic nucleus deep brain stimulation improves deglutition in Parkinson's disease. Mov Disord 23: 676–683. 2008

Erro R, Picillo M,et all. Non-motor Symptoms in Early Parkinson's Disease.J Neurol Neurosurg Psychiatry.84(1):14-17.2013

Hiyama T., Yoshihara M., Matsuo K., Kusunoki H., Kamada T., Ito M., Tanaka S., Nishi N., Chayama K., Haruma K. Meta-analysis of the Effects of Prokinetic Agents in Patients With Functional Dyspepsia. J Gastroenterol Hepatol. 22(3):304-310. 2007

Lim, S.Y. and Lang, A.E. The nonmotor symptoms of Parkinson's disease – an overview. Mov Disord 25(Suppl.1): S123–S130.. 2010

Magerkurth C, Schnitzer R, Braune S: Symptoms of autonomic failure in Parkinson's disease: prevalence and impact on daily life. Clin. Auton. Res. 15, 76–82. 2005

Parsons, T.D., Rogers, S.A., Braaten, A.J.,Woods, S.P. and Tröster, A.I. Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. Lancet Neurol *5:* 578–588. 2006

Ramaker C.; Marinus J., Stiggelbout A.M., van Hilten B. J "Systematic evaluation of rating scales for impairment and disability in Parkinson's disease". Movement Disorders 17 (5): 867–876. 2002

Rupam B, Rukmini M K, Afshan J, et all, Nonmotor Outcomes in Parkinson's Disease. Ther Adv Neurol Disorders. 5(1): 23-41. 2012

Schmulson M., Chang L., The Treatment of Functional Abdominal Bloating and Distension. Aliment Pharmacol Ther.;33(10):1071-1086. 2011

Tateno, F., Sakakibara, R., Yokoi, Y., Kishi, M., Ogawa, E., Uchiyama, T. et al.Levodopa ameliorated anorectal constipation in de novo Parkinson's disease: the QL-GAT study. Parkinsonism Relat Disord, 24 June, 2011