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Gastrointestinal Dysfunction in Parkinson's Disease

Klaus Krogh

*Department of Hepatology and Gastroenterology V, Aarhus University Hospital
Denmark*

1. Introduction

Swallowing difficulties and constipation were included in the first description of Parkinson's syndrome from 1817 (Parkinson 1817). Since then, numerous studies have confirmed the magnitude of symptoms and addressed their pathophysiology. In spite of this, much remains to be determined and treatment of gastrointestinal dysfunction in Parkinson's disease (PD) is often unsatisfactory.

Parkinson's disease is now considered a multiorgan syndrome (Den Hartog 1960; Eadie 1963; Ohama and Ikuta 1976) and gastrointestinal dysfunction is one among a number of other complications. Gastrointestinal symptoms affect the quality of life of many patients with PD and altered gastric and small intestinal transit may cause unpredictable absorption of medication further aggravating the classical motor symptoms of PD. The severity of gastrointestinal dysfunction in PD is often closely associated with progression of the disease in general. This makes treatment even more difficult as the patient may be severely handicapped by motor and general autonomic symptoms. In spite of recent progress, the conclusion from the latest Cochrane review on treatment of bowel dysfunction in central neurological diseases still holds true: "Bowel management for these people must remain empirical until well-designed controlled trials with adequate numbers and clinically relevant outcome measures become available" (Coggrave 2006).

2. Normal gastrointestinal function

2.1 Gastrointestinal transit

Transit through the gastrointestinal tract depends on a number of factors of which contraction of muscle cells and coordinated function of sphincters are the most important. While most of the gastrointestinal tract consists of smooth muscle cells, the oral part of the oesophagus at one end and the external anal sphincter at another are striated muscles.

Contraction patterns of the stomach and the small intestine depend on time since last meal. The postprandial or feeding pattern consists of irregular contractions promoting mixing and absorption. The interdigestive or fasting pattern starts approximately three hours after a meal. It serves to empty the stomach and clear the intestine of mucus, bacteria and debris. The interdigestive phase consists of runs of strong propulsive contractions approximately every 90 minutes. Gastric emptying is faster for liquid than for solid content but it is usually less than four hours while the normal small intestinal passage is less than six hours. Transit

through the colorectum is much slower than through the small intestine. Normal colorectal transit is usually less than three days. The colon is characterized by two types of contractions: localized (also termed haustral) contractions and high amplitude propagating contractions (also termed mass contractions). Haustral contractions occur all the time and serve to mix contents. Mass contractions occur a few times each day and propel stools over large distances in the colon. They often initiate defecation.

2.2 Normal defecation

Defecation depends on coordinated interaction between the colorectum, the puborectalis muscle and the anal sphincters. When mass contractions move stools to the rectum the rectal wall is stretched. This causes relaxation of the smooth muscle internal anal sphincter but contraction of the rectum itself, changing its properties from a reservoir to a conduit. Rectal contractions are further enhanced by the defecation reflex through the sacral segments of the spinal cord. The puborectalis muscle is relaxed thereby straightening the rectoanal angle and allowing passage from the rectum through the relaxed anal canal. If the striated external anal sphincter muscle is not contracted defecation takes place. The process is usually supported by a Valsalva manoeuvre. If any of the steps involved in defecation are impaired defecation becomes incomplete. This is felt by the subject as difficult defecation and an unpleasant feeling of residual stool in the rectum.

3. Gastrointestinal function in Parkinson's disease

3.1 Parkinson's disease and neuromuscular control of gastrointestinal transport

The basis for normal gastrointestinal transport is coordinated contraction of smooth muscle cells. Gastrointestinal smooth muscle cells contract when the membrane potential becomes more positive than -50 milli Volts. The frequency of contraction is determined by the interstitial Cells of Cajal, also termed gastrointestinal pacemaker cells. The smooth muscle cells are connected by gap-junctions making them function as a syncytium. Contractions and local reflexes are coordinated by the enteric nerve system located in the bowel wall. The enteric nervous system consists of approximately 10^8 neurons and a large number of neurotransmitters are found within it. One of these is dopamine. The direct effect of dopamine is inhibition of cholinergic transmission via D2 receptors (Walker 2000, Anlauf 2003). However, the *in vivo* result may be the opposite as there are indications that dopamine stimulates gastric and colonic contractions, possibly through other receptor types (Vaughan 2003).

Levi bodies are found in the enteric nervous system of patients with PD (Kupsky 1987, Wakabayashi 1990) and the concentration of dopamine in the colon is also reduced (Singaram 1995). This strongly indicates that enteric neurodegeneration as part of the multisystem involvement is a major factor in the pathogenesis of bowel dysfunction in PD. Also, there are indications that constipation in PD is associated with parasympathetic i.e. vagal dysfunction (Wang 1993).

3.2 Dysphagia in Parkinson's disease

Abnormal swallowing is found in 50 to 95% of patients with PD (Bushmann 1989, Logemann 1975, Nowack 1977). In most patients this causes no or only minor symptoms, but when severe, dysphagia may cause pain and discomfort. In very severe cases dysphagia causes insufficient intake of food and medication. Dysphagia in PD is mainly due to

insufficient cricopharyngeal relaxation and reduced oesophageal peristalsis (Eadie and Tyrer 1965 a, Nowack 1977). Insufficient chewing due to stiffness of the masticatory muscles may contribute to symptoms (Eadie and Tyrer 1965 b).

3.3 Gastric and small intestinal dysfunction in Parkinson's disease

Gastric emptying of solids is prolonged in 88% of patients with PD and 38% have delayed emptying of liquids (Goetze 2006, Hardoff 2001). Accordingly, nausea and bloating are more frequently reported by patients with PD than by healthy controls (Edwards 1991). Delayed gastric emptying is associated with motor response fluctuations, probably due to unpredictable absorption of medication (Djaldetti 1996). Also, delayed gastric emptying is associated with use of levodopa (Hardoff 2001). Small intestinal transit in PD has only received little attention. In a single study using the hydrogen breath test patients with PD had longer than normal small intestinal transit time (Davies 1997). In the same study there was no sign of small intestinal bacterial overgrowth. As indicated, gastric emptying and small intestinal transit are important in PD not only because of gastrointestinal symptoms but also because they have profound effects on levodopa absorption.

3.4. Colorectal and anal sphincter dysfunction in Parkinson's disease

Constipation is the most prominent bowel symptom in PD. It is a syndrome whose two main components are infrequent defecation and difficult rectal evacuation. The former mainly reflects slow colorectal transit and the later abnormal dynamics at defecation.

Infrequent defecation is commonly defined as two times or less per week. Following this definition between 35% and 81% of patients with PD have infrequent defecation (Edwards 1991, Sakakibara 2001, Siddiqui 2002, Singer 1992, Ueki 2004). Comparing patients with PD to age adjusted control groups, PD patients have significantly less frequent defecation (Edwards 1991, Krogh 2008, Sakakibara 2001, Singer 1992) and more than one third regularly use oral laxatives (Eadie and Tyrer 1965, Krogh 2008, Singer 1992). It is likely that infrequent defecation is caused by enteric neurodegeneration in the colorectum. Accordingly, colorectal transit times, determined by the intake of radioopaque markers and subsequent abdominal x-rays, are prolonged in patients with primary PD (Jost and Schimrigk 1991, Edwards 1994, Sakakibara 2003) but not in those with non-idiopathic PD secondary to cerebral infarcts (Jost 1994).

Symptoms of difficult rectal evacuation are very common in PD (Edwards 1991, Krogh 2008). A subjective feeling of incomplete evacuation is reported by 23% and 17% need some sort of assisted defecation (digital evacuation, suppositories or mini enema) at least once per week (Krogh 2008). Studies with anorectal manometry have unambiguously shown that patients with PD and difficult defecation have dystonia of the external anal sphincter muscle (Ashraf 1995, Bassotti 2000, Edwards 1994, Mathers 1988) and puborectalis muscle (Mathers 1988). In contrast to normal external anal sphincter and puborectalis muscle relaxation at defecation, patients with PD have paradoxical contraction. This obstructed defecation is the other main reason for constipation related symptoms in PD. In a comprehensive study of rectoanal physiology in PD rectal sensation to distension and rectal compliance were normal, but rectal contractions had significantly lower amplitude and there were significant post-defecation residuals (Mathers 1989, Sakakibara 2003). Reduced straining due to motor dysfunction may contribute to reduced colorectal transport at defecation (Sakakibara 2003). Some patients with PD have faecal incontinence, but compared to age matched control groups the prevalence is not increased (Krogh 2008, Singer 1992).

3.5 Gastrointestinal symptoms and severity of Parkinson's disease

Infrequent defecation in otherwise healthy men is associated with increased risk of developing PD in later life. In a large American population based study mid aged men with bowel movement less than once per day had a 2.7 fold risk of developing PD within the next 24 years when compared to those with daily bowel movements (Abbott 2001). The information is of little clinical use, but underlines the multiorgan involvement in PD: in some the disease starts in the central nervous system in others it begins in the bowel. Several studies have confirmed that symptoms of constipation are strongly associated with the severity of PD assessed by the Hoehn and Yahr staging (Eadie and Tyrer 1965, Edwards 1991, Krogh K 2008, Sakakibara 2001). It is also likely (Eadie and Tyrer 1965, Edwards 1991) but fully established (Bushman 1989) that chewing difficulty and dysphagia are associated with increased severity of PD.

4. Evaluation of gastrointestinal symptoms in Parkinson's disease

Evaluation and treatment of swallowing disorders in PD are beyond the scope of the present chapter.

4.1 Evaluation of gastric and small intestinal function in Parkinson's disease

The gold standard for gastric emptying and small intestinal transit is scintigraphy with the liquid and the solid phase marked with each their isotope (Goetze 2006). The method is expensive and demands access to a gamma camera. It is therefore only used in a minority of patients. Absorption of paracetamol occurs in the duodenum and systemic absorption is therefore an indirect measure of gastric emptying of liquids. The method is of limited value in PD as most patients have delayed emptying of solid but not liquid contents. The wireless motility capsule (Kloetzer 2010) or the magnet based Motility Tracking System (Fynne 2011) may become clinically important alternatives. Endoscopy is indicated if structural changes or malignancy is suspected.

4.2 Evaluation of colorectal and anal sphincter function in Parkinson's disease

No standardized instrument for assessment of colorectal symptoms in PD exists. The Cleveland Clinic constipation scoring system is often used (Agachan 1996), but it has not been formally evaluated in patients with neurological diseases. A neurogenic bowel dysfunction score has been developed for description of bowel symptoms in patients with spinal cord injury (Krogh 2006), but it is not valid in PD (Krogh 2008). A thorough anamnesis is therefore of paramount importance. Questions have to be specific and directly asked. Otherwise, symptoms will be underestimated. Important items are: Frequency of defecation, consistency of stools, number of unsuccessful attempts at defecation, time for each bowel movement, pain at defecation, need for digital evacuation of stools, a sense of incomplete defecation, abdominal pain, use of oral or rectal laxatives, bloating and blood in stools. Also, side effects to medication, including medication against PD, must be considered. Diet and fluid intake must be assessed. However, there is no evidence that the diet of constipated patients with PD differs significantly from that of asymptomatic controls (Edwards 1991).

In most patients treatment can be initiated just based on the anamnesis. Some bowel symptoms attributed to PD may be caused by colorectal cancer, especially if they have developed over a short period of time. Therefore, anorectal digital examination and endoscopy are relevant in a number of cases. In cases with severe symptoms not

responding to first-line treatment determination of colorectal transit time and anorectal physiology tests may be performed. Colorectal transit time, or more correctly termed total gastrointestinal transit time, can be assessed from the intake of radioopaque markers followed by one or more plain abdominal X-rays. A number of protocols exist. In general, the number of markers left after a specific number of days is counted. If only a single dose of markers (usually 24 small plastic rings) is taken and this is followed by a single x-ray the information is qualitative – transit time is either normal or prolonged. If markers (usually 10) are taken on a number of days (often six) before the x-ray is taken total transit time can be computed in days (Abrahamsson 1988). Also segmental transit times of the ascending colon, the transverse colon, the descending colon and the rectosigmoid can be computed. The advantages of radiographically determined colorectal transit time are that it is easy to perform, it provides an objective measure and it can be performed before and during treatment. The disadvantages are that intersubjective variation is very large and that the correlation between results and bowel symptoms in patients with PD is poor (Edwards 1994, Jost 1991). Examples of radioopaque marker studies are shown in figure 1.

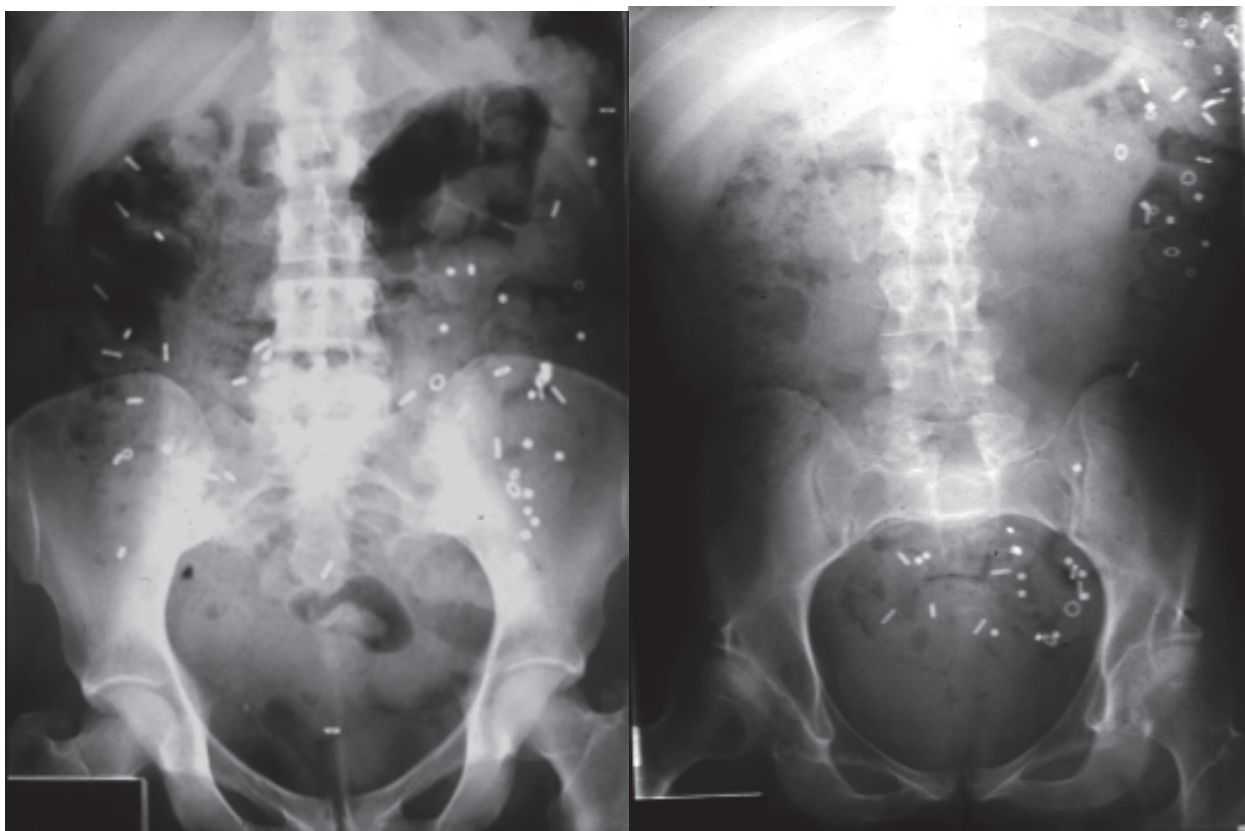


Fig. 1. Examples of radiographically determined colorectal transit times. Ten marks were taken each day on six consecutive days and an abdominal x-ray was taken on day seven. In healthy subjects there will be no more than 23 markers left. In the subject on the left the number of markers is increased and they are scattered throughout the colon. This indicates generally slow colonic transit. In the subject on the right the number of markers is also increased but the are mostly located in the left colon and the rectum. This indicates difficult evacuation at defecation.

Anorectal physiology tests are only performed in a minority of patients with PD. The most common tests are manometry of the anal canal at rest and during squeeze, sensation during rectal balloon distension and anal manometry at attempted defecation of a balloon (Ashraf 1995, Edwards 1994, Mathers 1988). The later test is the most important in patients with PD as it may reveal abnormal contraction of the external anal sphincter during attempted defecation. Evacuation proctography is performed after installation of barium contrast in the rectum. The subject is seated on a commode in front of the camera and videoradiography is taken during attempted defecation. The method may show structural changes during defecation and it gives a semi-quantitative description of incomplete evacuation. It is, however, rarely performed in PD. New methods such as evacuation scintigraphy may have a future clinical role (Krogh 2003).



Fig. 2. Rectal balloon expulsion test. Pressure or EMG activity is registered in the anal canal while the subject tries to expel a balloon from the rectum (top). Under normal circumstances there is no increase in anal pressure or EMG activity (middle). In patients with Parkinson’s disease there is paradox contraction of the external anal sphincter (bottom).

5. Treatment of gastrointestinal complications in Parkinson's disease

There are strong indications that levodopa may reduce dysphagia (Bushman 1989, Logemann 1975) and constipation in PD (Krogh 2008). This is probably because levodopa reduces dystonia of the striated muscle cells of the upper oesophagus and the external anal sphincter. Levodopa is absorbed in the duodenum and proximal ileum. Increased intake of insoluble dietary fibre not only alleviates constipation in PD patients (Astarloa 1993) but also increases the bioavailability of levodopa (Astarloa 1993, Garcia 2005 a+b). Use of levodopa is, however, associated with prolonged gastric emptying. Symptoms of delayed gastric emptying can be treated with the dopamine antagonist domperidone which does not cross the blood-brain barrier (Shindler 1984, Soykan 1997). In contrast, dopamine antagonists that cross the blood-brain barrier, including metoclopramide and levosulpiride, should not be used in PD as they may worsen motor symptoms. Constipation can be alleviated with polyethylene glycol (Eichhorn 2001) or polycarbophil (Sakakibara 2007). Serotonin 5-HT₄ receptor agonists including cisapride (Djaldetti 1995), tegaserod (Sullivan 2006) and mosapride (Liu 2005) may relieve constipation and reduced colonic transit time in patients with PD. Cisapride is now rarely used because of risk of cardiac arrhythmias and the clinical role of the other agents remains to be established. Many patients with PD use standard oral laxatives, suppositories and mini enema. Even though the use of such "older" agents is widespread their effects remain to be studied in clinical trials. Pilot data on Botulinum toxin A injections for relaxation of the puborectalis (Cadeddu 2005) or biofeedback for relaxation of the external anal sphincter muscle (Chiarioni 2006) in PD have been performed, but more data are needed to draw conclusions about future use. Other methods commonly used for bowel dysfunction in other groups of patients with neurological disease include transanal irrigation through a catheter inserted in to the rectum (Shandling and Gilmour 1987), the Malone antegrade continence enema through a small stoma created from the appendix (Malone 1990), sacral nerve stimulation (Kamm 2010), and colostomy. There is not enough evidence to recommend any of those methods for use in PD and they must until further be considered experimental.

6. Conclusions

Parkinson's disease is a multi-system disorder including gastrointestinal dysfunction. Most gastrointestinal symptoms in PD can be attributed to dystonia of the striated muscle cells in the oesophagus and anal canal and to reduced stimulation of the smooth muscle forming the remaining part of the gastrointestinal canal. No guidelines to evaluation and treatment of gastrointestinal dysfunction in PD exist and evidence for treatment is generally poor. The majority of patients can be treated based on a thorough anamnesis. Initial treatment will often be increased fibre intake and oral laxatives. Advanced treatment of severe constipation in PD is still experimental.

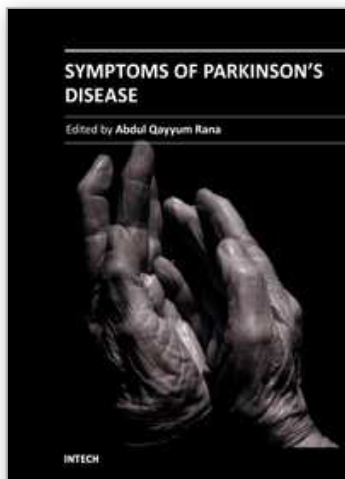
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This book about Parkinson's disease provides a detailed account of various aspects of this complicated neurological condition. Although most of the important motor and non-motor symptoms of Parkinson's disease have been discussed in this book, but in particular a detailed account has been provided about the most disabling symptoms such as dementia, depression, and other psychiatric as well as gastrointestinal symptoms. The mechanisms responsible for the development of these symptoms have also been discussed. Not only the clinicians may benefit from this book but also basic scientists can get enough information from the various chapters which have been written by well known faculty.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

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InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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