

OLD HERBORN UNIVERSITY SEMINAR ON GASTRO-INTESTINAL MOTILITY: REVIEW OF THE INTERNAL DISCUSSION

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INTRODUCTION

During the internal discussions which followed the oral presentations which were held on 26 June 1995, a selected group of scientists, enlisted above, exchanged ideas and recent findings in the field of gastro-intestinal motility. One of the main subjects concerned the current status of the method-

ological set.

The discussion on methodology followed the anatomy of the gastro-intestinal tract (GIT). Several methods concerning a range of both anatomical and functional tests were discussed in an organ-oriented fashion.

METHODOLOGY FOR MEASURING GASTRIC MOTILITY: THE STOMACH

Scintigraphy

Scintigraphy is an accepted method for monitoring of gastric emptying. It can be used for solid material: egg omelette or pancake, sometimes radio-labelled with Gallium or Technetium. (Note: Flower in pancake prevents binding of radiolabel).

Once the label is ingested, two camera's in sandwich position are used to measure the pattern of gastric emptying. The correlation between retardation gastric emptying and pathologic disorder is unfortunately still low. The advantage of the test is its convenience for both patient and doctor. A disadvantage concerns the use of radiolabels.

Paracetamol absorption

In this test the levels of paracetamol which appear in the blood stream after oral intake of a standard dose of paracetamol are measured. Paracetamol absorption is still an experimental method. Paracetamol is nearly completely absorbed in the duodenum. However, it is weakly acidic so that a small part of the dose is already absorbed in the stomach. In a healthy person, paracetamol can appear in the blood stream after 10 minutes. The period of measuring paracetamol levels in the blood after oral intake, should not exceed 90 minutes because after that time period paracetamol is being metabolized by the host.

(Note: A problem is that normal liquid emptying may be confused with pathological solid emptying. One has to make sure that no solid material is in the stomach when this test is performed).

H₂-breath test

In this method, after intake of an omelette labelled with C¹³, the amount of exhaled H₂ is determined. This method is fast, cheap and the results correlate very well with the results of scintigraphy. Therefore this method is used both in research and in clinical settings.

Ultra sonography

Ultra sonography renders the possibility to image the boundaries of the empty compartment of the antrum pylori. In order to obtain sharp boundaries in the image, only liquid emptying is monitored. However, because this method has not been validated properly, it is only employed in research

Analysis of a "gastric emptying curve"

The half-life time of emptying is the time required to reduce gastric contents with 50%. To make the outcome reliable, the entire gastric emptying curve needs to be recorded. Furthermore, this parameter is not very indicative as the gastric emptying is not constant.

The slope of the curve at a defined point in time after the start of the mea-

surement or at the linear part of the curve could also be used as a measure. This method, however, also depends strongly on the constancy of the gastric emptying rate. This type of evaluation has the advantage that only a portion of the curve needs to be recorded.

Antro-duodenal manometry

This method involves measurement of pressure differences in the antro-duodenal region. Especially the pressure induced by motor activity of the stomach during feeding may be of functional value. (Note: A problem with this method is that the catheter with its pressure-sensitive points may slide out of position into the stomach during motor activity. During feeding the stomach increases in size. The influence of this phenomenon on manometric patterns is not clear yet).

Using scintigraphy it can be seen that only 40% of the contractions is actually recorded by this method. This method only used in research centres to measure the postprandial motor patterns because of their clinical importance.

Electro-gastrography

This method of measuring myogastric activity is using electrodes placed on the outer side of the body. It is a convenient method for the patient. The method yields a cyclic signal (2.7 cycles/min). Interpretation of the data (expressed in mV/cm²) is difficult

THE SMALL INTESTINE

Scintigraphy of the small intestine

Scintigraphy is probably a useful method. However, the anatomical overlap of the various parts of the small intestines is a problem; this may cause difficulties during image-interpretation. In addition, the method is not validated.

H₂-breath test

With oral lactulose, this test gives a good indication of the absorption capabilities of the small intestine. (Note: A problem with this test concerns the fact that measurements are hampered by the fact that lactulose increases the duodenal transit time. The result of the method

need to be corrected for this phenomenon).

This method is only employed for research applications, e.g. for drug response testing and for manometry of the duodenum. It is the most frequently used test method at this moment; both in clinical practice and in research. The method can be applied both in a stationary and in an ambulatory setting; the latter yields a lot of noise in the data set.

The motor patterns obtained with this method allow differentiation between feeding and fasting patterns. An occasional pathological pattern has as yet no clinical meaning.

Statistical analysis of the manometry data of the duodenum is particularly useful. The data can be divided in three phases (phase I, II and III). All phases are probably related to a contraction stage. The use of combinations of one or more of these parameters provides

combination parameters which may yield information that is easier to analyse with standard statistical methods. An example of the advantage of this method is the fact that "hidden phase III" activity (which is not visible in the raw data) may be detected.

Some manometrical observations important for pathology

PCC (propagated cluster contractions) are observed in the elderly, during irritable bowel syndrome (IBS) and during diarrhoea. Isolated bursts in upper small intestine are indicative for "bacterial overgrowth". Giant migrating bursts in upper small intestine and "bacterial overgrowth" are likely related to one or even several infecting agents. This concerns an influence of bacteria on motor patterns probably not caused by endotoxins.

THE COLON

Methods concerning the functioning of the colon can be divided in two functionally different groups:

- a. Flow-measurements: scintigraphy and marker transit
- b. Wall movements: radiology, manometry, barostatic measurement and EMG.

Scintigraphy and marker transit

This method (intake of 20 plastic pellets daily during 6 days, measurement of the location of the pellets with scintigraphy) can only be performed when the anatomy of the gastrointestinal tract is normal.

This method provides a quantitative measure for the colonic transit time. Obstipation can be quantified in this way. (Note: A problem is that method is nearly always employed in sick and/or old people. The obstipation measured

may then be a secondary result of immobilization or drugs used for treatment).

During the discussion it was stated that the colonic flora itself has no influence on the flow-rate. Increased production of fatty acids by colonic flora will enhance the flow-rate (diarrhoea) but a possible (inhibitory) static effect could not be explained.

Manometry of the colon

Manometry of the colon is not used very often; no clear method for the analysis of the data is available today. Only rectal data are usable. (Note: A disadvantage is that the colonic lumen is in fact too wide; this gives poor data. The contraction rate may be higher during diverticulae. The colon has to be cleansed before manometry can be used).

Barometry of the colon

A barometer measures volume rather than pressure. The colon does not have to be empty. This technique is mostly employed to measure contractions in the rectal sigmoid area. Standardization of data is not yet possible.

Myoelectrogram

This technique concerns the measurement of the slow electrical waves which traverse the colon. There is as yet no clinical application. Data interpretation is very difficult.

MICROBIAL PRODUCTS AND MOTILITY

The kallikrein-kinin system

The kallikrein-kinin system, was originally identified by *Gordon* and colleagues as an utero-contractile and a villi contractile substance. Thus far only the influence of the system on colonic motility of the cat is studied. It appears that the system is present in the entire gastro-intestinal tract. *Bruckner* presented a scheme in which an influence on the α -pigment receptor is proposed.

Short chain fatty acids (SCFA)

Short chain fatty acids (SCFA) are produced by the anaerobic microflora in the colon. Testing of several concentrations (after oral feeding) of SCFA in germfree and in conventional mice revealed a short-term increase of the motor complexes (MMC) along the intestinal tract. However, all animals showed quick adaptation to the elevated levels of SCFA and returned to normal MMC-values, even when intestinal SCFA-levels remained high. It is thought that SCFA's have a modulating effect on the enteric nervous system (receptors unknown). This may explain the rapid adaptation. Especially butyric acid seems to have an effect. (*Husebye* proposed implantation of butyric producing *E. coli*). Propionic acid would stimulate pancreas secretion.

Poly-unsaturated fatty acids (PUFA)

Germfree animals have higher levels of poly-unsaturated fatty acids (PUFA)

in the enterocyte membrane. The function is unknown

Prostaglandins

No experience on the effect of prostaglandins was available. *Husebye* reported on an experiment in which the influence of NO, eicosanoids and prostaglandins on the immuno-histochemistry of the gut associated lymphoid tissue of germfree mice was tested. This appeared to have no microscopical effects.

Macrolides

Macrolides are antibiotic-like substances produced by the gut-flora. Most studied is motilin, which causes MMC increase in animals. Hypothesis: Motilin binds an muscular receptor or an neuronal receptor.

Tests with motilin antagonist ANQ-11168 are in progress; motilin is administered intra-nasally.

Serotonine

Serotonine has a strong gut motility normalizing effect. Serotonine is stored in the mucus but is metabolized very quickly. Serotonine can also be produced by the gut microflora. Which microorganism is responsible is not known. In humans, it is known that a substance (5H-tryptophane, synthesized by the reduction of tryptophane) has a serotonine-like effect. 5H-tryptophane is produced *in vivo* by *Entamoeba histolytica*.

Biliary products

Experiments in rats (surgical: outlet of bile, pharmaceutical: stimulation by oral mannitol) show no influence of bile on the MMC's.

Endotoxins

The effect of endotoxin is difficult to measure because of the major side effects (multiple organ failure). There are no data available which make likely that there is an effect.

Nitric oxide (NO) and vaso-active intestinal peptide (VIP)

NO is produced in the muscular cells of the GIT. Arginin is converted to citrullin by NO-synthetase (the production is receptor mediated). NO is excreted and via a carrier molecule transferred to smooth muscle cells. In the smooth muscle cells, it induces muscle relaxation via the GMP second messenger system.

During the discussion a new hypothesis on the function of NO was proposed: NO is thought to give rise to the production of VIP (vaso-active intestinal peptide). Blocking of the VIP-receptor in nerve terminal blocks of the signal transduction, resulting in the absence of

MMC's and thus dilatation of muscle cells (*Mutt and Said*, New Engl. J. Med., 1970) Nowadays VIP (28 amino acids long) is regarded a neurotransmitter.

Other vaso-active substances

Other vaso-active substances are:

- Calcitonin (not a CNS-peptide),
- Neurotensin,
- Oxytocin (stimulates muscle contraction),
- Opiates (blocks muscle contractions),
- Somatostatin (effect on GIT unknown),
- GABA (probably not effective),
- Diazepam (blocks stimulator GABA activity) has no effect.

Criteria for gut motility promoting mediators

To name a substance a gut motility promoting mediator (GMPM) it should meet several criteria. The following three criteria were proposed:

1. Substance should be present in the gut lumen,
2. Substance has to provoke a response upon luminal application,
3. substances effect should remain intact upon removal of the gut flora.

PROBLEMS

In addition to the substance being tested, a multitude of other substances may interfere with the test system applied. The gastro-intestinal tract responds probably to any substance as long as its concentration is high enough.

In the colon, nearly no slow contractions do exist (the outflow would be to high). Only giant migrating bursts are known. This poses a methodological problem

The size of the caecum. The influence of the caecum on MMC's in gut-motility experiments on germfree and specified pathogen free (SPF) animals is remarkable (it is thought that the large volume of the caecal contents in these animals has, because of its bulk, a large disturbing influence on the gut motility). Tests in which such animals are used, are strongly biased by this phenomenon.