Childhood constipation: new insights in testing, treatment and cost
Liem, O.

Citation for published version (APA):
Liem, O. (2010). Childhood constipation: new insights in testing, treatment and cost
Summary and Future Perspectives
The prevalence of functional constipation in children is widespread. Although in most cases short-lived and easy to treat, constipation in some patients can be a very challenging disorder for both patients and care givers. In these cases patients are often referred to specialized centers for further diagnostic testing and treatment. The main problem is that the pathophysiology of constipation is not fully understood and that therapy is largely based on experience rather than evidence. Colonic manometry has taught us more about the pathophysiology of constipation and helps us in the management of children with severe constipation. But not all can be explained. This thesis focuses on the use of motility testing in this group of children and discusses further research studies on treatment and cost analysis of childhood constipation.

One of the tests often performed in children with severe constipation is colonic manometry. This test helps to differentiate functional constipation from constipation secondary to organic causes and can predict the success of antegrade enemas administered through a cecostomy. The presence of high amplitude propagating contractions (HAPCs) is of main interest since their presence has been identified as a marker of colonic neuromuscular integrity. Despite their important physiologic and diagnostic significance, little is known about the factors that initiate HAPCs. Physical factors such as luminal distention secondary to colonic filling have been hypothesized as physiologic initiators of HAPCs. Chapter 1 describes a study that evaluated the effect of intraluminal balloon distention in the colon of children with defecatory disorders, especially with respect to the initiation of HAPCs. The study demonstrated that intraluminal colonic distention was able to trigger propagated contractions in children. Although HAPCs were triggered in some children, colonic distention was not as consistent in inducing HAPCs as the motor response found in response to bisacodyl administration. Further studies are needed to further elucidate the mechanisms that are responsible for the initiation of propagating contractions, both HAPCs and low amplitude propagated contractions (LAPCs). Until further research is done into its clinical significance, colonic balloon distention in children should remain a research tool.

Colonic manometry is usually performed using a water perfused catheter. These open tipped catheters are connected to a pneumohydraulic infusion pump that ensures constant flow of water and are attached to cumbersome recording equipment. Developments in microtransducer technology have allowed the production of manometry catheters incorporating miniaturized strain gauge transducers. These catheters allow recording of gastrointestinal motor activity on portable solid-state data logging devices. In Chapter 2 we compared solid-state (SS) to the water-perfused manometry (WP), with particular attention to the detection and measurement of HAPCs. The results showed that solid state catheters connected to
a portable data logger seem more sensitive in recording HAPC in children compared to the more traditional water-perfused assembly. Solid-state catheters offer potential advantages over water-perfused catheters in children, being portable, safer to use and provide data over a more prolonged period of time. Further research should be done to address the higher costs and the criteria for HAPC detection using solid state catheters.

The standard protocol for measuring colonic motility consists of a four hour stationary colonic manometry testing. At least 1 hour of fasting and 1 hour of a postprandial motility is recorded after which drug stimulation with bisacodyl is performed if no HAPCs are observed during fasting or postprandially. There are a few drawbacks related to this procedure. For one, the measurement is highly non physiological since patients are immobile during the whole study and sometimes still stressed from the placement of the catheter. Secondly, this rather “short” measurement does not take into account the fact that colonic motility has a diurnal rhythm. **Chapter 3** describes a study that aimed to perform 24 hours studies in children with severe defecation disorders who were referred for colonic manometry studies.

Prolonged colonic measurement provided more information regarding colonic motor function and allowed detection of motor events missed by the standard short manometry study with provocation. Prospective follow-up studies are necessary to evaluate the clinical relevance of this information.

The prevalence of constipation seems to be higher in children who suffer from obesity compared to the general population. However, previous studies have, not used Rome III criteria, which makes them harder to compare to other studies with respect to childhood constipation. The etiology of the increased prevalence constipation in obese children is not clear. Several mechanisms have been proposed such as diet, hormonal changes, level of activity but no direct mechanism has been demonstrated yet. We were therefore interested to uncover whether these children actually had a delayed colonic motility.

In **Chapter 4** we describe a study in which we measured colonic transit time in morbidly obese children. We confirmed that a higher prevalence of childhood constipation in obese children exists using the Rome III criteria. We showed that the increased prevalence was not due to decreased colonic motility. The difference in prevalence could also not be explained by differences in diet, especially not in the fiber or fat intake. Therefore more studies are needed to elucidate the relationship between constipation and obesity in children as other factors such as hormones and exercise may also play a role.

The treatment of children with chronic constipation can be challenging and may lead to disappointing results for both child/parents and physicians. Thus, it is crucial to be familiar with treatment modalities that go beyond traditional and standard care. **Chapter 5** provides an overview of novel and alternative therapies, such as probiotics,
new drugs and surgery, that are currently being proposed for the treatment of childhood chronic constipation. Although some therapies seem very promising, large randomized controlled studies are lacking making it difficult to make evidence-based recommendations.

One of the potential new drugs for constipation was tegaserod. Tegaserod (5-hydroxytryptamine) is a selective serotonin receptor agonist that acts at 5-HT₄ receptors in the gut wall. The central role of serotonin in modulating motility, visceral perception, and intraluminal secretion in the gastrointestinal tract makes the serotonergic system an important therapeutic target. In Chapter 6 we describe our experience with tegaserod. We found that tegaserod contributed to the relief of a variety of functional gastrointestinal symptoms, such as constipation, abdominal pain and bloating in children with a heterogeneous group of severe gastrointestinal symptoms. Unfortunately, tegaserod was pulled of the market due to a meta-analysis that showed an increase in cardiac events in adults and can now only be prescribed for compassionate use. Hopefully, lubiprostone and prucalopride, two other potential new drugs shown to be effective in adults, will be proven to be as successful in children.

Due to its wide prevalence and chronic nature, it has become clear that constipation is a significant source of health care expenses and a potential target for reducing health care cost. Chapter 7 describes a study that shows that childhood constipation has a significant impact on the use and cost of medical care services among children in the United States. The estimated US dollars cost per year is 3 times higher compared to children without constipation and probably still underestimates the real burden of childhood constipation. Our data suggest that the burden of illness imposed by constipation, and the costs associated with this condition, are roughly of the same magnitude as for asthma and ADHD. We therefore believe that constipation deserves similar emphasis and justification exists to promote public health efforts to improve its prevention, recognition, and treatment.
FUTURE PERSPECTIVES

The use of the Rome III criteria has improved the clinical recognition of constipation and makes it possible to compare research data and stimulates collaboration between fields. The exact pathophysiology of functional constipation, however, is still unknown. It is likely that multiple factors are involved in the development and persistence of functional constipation and it is important to continue to investigate them in the future.

The burden of childhood constipation is high. Economically, as has been shown in this thesis, but also emotionally leading to a lower health related quality of life as demonstrated by long term follow-up studies from our motility unit. Further research is necessary to establish the underlying pathophysiology and to create validated diagnostic tools. This may lead to therapies that are not only based on empiric data and might be more successful than the ones currently employed.

Colonic manometry has given us a direct way to investigate the colon and has increased our knowledge of colonic motor physiology. Several studies have demonstrated the clinical usefulness of measuring colonic motility in children with intractable constipation but this technique has its limitations. An important shortcoming remains the lack of normal values from a healthy control group. Unfortunately these will not very likely to become available due to ethical obstacles to perform such invasive tests in healthy children. Furthermore, the existence of colonic neuromuscular disorders cannot be identified based on colonic manometry studies alone. The interpretation of colonic manometry studies is therefore difficult and physiological significance of some contractile activities identified by manometry continue to be uncertain. For example: a small subgroup of children will do well even without high amplitude contractions (HAPCs) or will not do well with "normal" motility found by colonic manometry. Increased understanding of this complex system is concomitant with advances in methodology and 24 hours manometry could possibly shed more light in those cases since it detects more motor events. Other interesting new developments are manometry studies using fiber optic catheters with very closely spaced sensors (10mm apart) allowing a full interpolated image of intraluminal pressure to be generated. Wireless capsule measurements of motility is another new technique that has not been researched extensively in children yet. Prospective longitudinal studies are required to evaluate the clinical meaning and studies should, at present, be limited to specialized centers.

In this thesis we described an increased prevalence of constipation in morbidly obese children. Associations between constipation and other diseases have been observed in both adults and children. However, not much is known about the mechanisms...
behind these associations. Related conditions range from gastrointestinal complications, urologic disorders and more recently autism.\textsuperscript{5-7} The big challenge is to further investigate these associations in order to unravel the mechanisms behind them. Studies looking at the relationship of constipation with urological symptoms and with autism are currently in progress in our motility unit and will hopefully increase our understanding.

Development of new treatment strategies is challenging but necessary given the fact that a subgroup of children fail to achieve successful clinical outcome. Due to lack of published data pediatricians are often faced with the dilemma of either treating children with potentially harmful medications based on data extrapolated from adult studies or withholding potentially beneficial therapies. This was also the case with the use of tegaserod, a selective serotonin agonist that was shown in adult data to be beneficial for several gastrointestinal complaints. All children in our study received tegaserod off-label since no previous studies in children had been done. In general, studies show that over 50% of the compounds used in children have not been tested for use in this specific age group. The absence of suitable authorized compounds to treat conditions in children results from the fact that pharmaceutical companies frequently do not perform the necessary research and development to adapt medicinal products to the needs of the pediatric population. Hopefully new regulations both in the United States and European Union will improve this problem. These regulations set up a system of requirements, rewards and incentives, to ensure that compounds are researched, developed and authorized to meet the therapeutic needs of children.
REFERENCES


