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Pitfalls in designing trials of functional dyspepsia: the ascent and demise of itopride

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The publication in this issue of *Gut* (***see page 740***) of the results of the clinical trial programme evaluating itopride in functional dyspepsia (FD)[1] needs to be applauded on two counts:

- Axcan Pharma, the sponsor of the study for conducting this comprehensive clinical trial programme.
- *Gut* for publishing data that are important despite the overall disappointing results of the studies.

Over the last 15 years, definite progress has been made in the design, execution and data analysis of FD treatment trials. The efficacy of a limited number of treatment options has also been established. There is evidence that proton pump inhibitors (PPIs), and to a lesser extent H_2 receptor antagonists (H_2RAs), are efficacious in a proportion of FD patients.[2–5] Importantly, the presence of heartburn appears to be a predictor of response.[2] As a result, there is debate as to whether this is due to the inclusion of patients with unrecognised gastro-oesophageal reflux disease (GORD) symptoms rather than "true" FD patients.[6] Consequently, there is a school of thought that non-response to a PPI should be a diagnostic criterion for a diagnosis of FD. In a small proportion of *Helicobacter pylori*-positive FD patients, cure of the infection will lead to a sustained improvement in symptoms with an estimated number needed to treat to obtain one success of 14.[4 5 7]

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There has been a longstanding interest in the use of prokinetics, especially cisapride, as a treatment for FD. Unfortunately many of the cisapride studies suffered from poor study design, and there is evidence that this tended to overestimate treatment efficacy.[4 5 8]

Furthermore, it is possible that part of the response seen with cisapride in FD may have been related to associated heartburn symptoms.[8] A systematic review on the use of cisapride for GORD in children also suggested evidence of publication bias.[9] A similar finding was observed in adult cisapride non-ulcer dyspepsia trials.[5]

Itopride, a benzamide derivative, exerts its activity by inhibition of the dopamine D2 receptor and acetylcholinesterase.[10 11] It should be stressed that the basic scientific evidence that itopride has efficacy as a prokinetic agent is weak at best. Itopride is currently available on the market in Japan indicated for the treatment of upper gastrointestinal tract disorders. Axcan Pharm embarked on a phase II and III multicentre and multinational clinical trial programm,e that involved >1700 patients. The phase II trial, labelled as positive, received particular attention through its publication in the *New England Journal of Medicine*.[12] The results of the two simultaneously conducted phase III clinical trials involving 1170 patients are reported in this issue (***see page 740***) and did not show efficacy of itopride.[1]

In order to analyse the data and put the findings in perspective, study design issues are important. There now is consensus that the main outcome measure in FD trials should be the proportion of patients who achieve an a priori stipulated amount of improvement in symptoms. The Rome Working Parties on the Design of Clinical Trials proposed that either a global outcome measure be used or a summary score of a previously validated questionnaire that assesses the relevant FD symptoms.[13 14]

In the itopride phase III trials, two primary outcome measures were used. (1) A 5-point global patient assessment (GPA) scale measured change ranging from (a) symptom-free, (b) markedly improved, (c) slightly improved, (d) no change, and (e) deteriorated. A patient was classified as a responder if they became symptom free or reported marked improvement. (2) Two questions of the Leeds Dyspepsia Questionnaire (LDQ)—that is, severity of abdominal pain and fullness—measured on 6-point scales ranging from 0 = absent to 5 = a very severe problem. The complete LDQ was used as part of the inclusion criteria. The LDQ measures eight dyspepsia symptoms in three domains: gastric (epigastric pain, fullness, belching), oesophageal (heartburn, regurgitation and dysphagia) and feeling sick (nausea, vomiting); it has a summary score range of 0–40.[15 16] One could argue that it is somewhat problematic to choose the LDQ as a primary outcome measure as reflux symptoms were reasons for exclusion.

Did the phase II truly show benefit for itopride?[12] A clear weakness in the study was that it was not stated what amount of improvement in the LDQ was considered to be clinically significant. The observed change in LDQ score between active treatment and placebo of 1.77 (6.27 for a three times daily 200 mg dose of itopride vs 4.5 on placebo), although statistically significant, was unlikely to be clinically meaningful, given that the scale range is 0–40. It is also important that study reports clearly document the proportion of patients in whom symptoms have completely disappeared, as this outcome will have the lowest placebo response. This then gives one a better estimate of true effect size, assuming there was superiority of the active treatment. In the phase II trial, no data on

GPA results were provided for the proportion of patients that were completely asymptomatic. Instead only the composite score of those patients who became asymptomatic or markedly improved were reported. For this end point, there was a significant difference of 41% for placebo compared with 57–64% for varying doses of itopride. As already mentioned, potential overlap between GORD and dyspepsia is important, as it may be a predictor of response. In the phase II trial, 18–22% of entered subjects did have heartburn as a symptom, but it is unclear how frequent or severe these reflux symptoms were although it was stated they were subordinate to epigastric pain.

Not all these criticisms apply to the report of the phase III studies. The exclusion criteria for heartburn were much stricter, in that patients could not have heartburn more than once a week, and this could not be more severe than epigastric pain or discomfort. Nevertheless it remains debatable whether it was sufficient that patients were off acid suppressive therapy in the 20 days prior to randomisation. Oesophagitis remains a frequent reason for exclusion in FD trials even though this may not be obvious based on symptoms.[17 18] It is well known that reflux symptoms or oesophagitis can reappear >20 days after acid suppressive therapy is stopped. On the other hand, it is acknowledged that study entry criteria need to be practical. Certainly one would like to exclude patients who were responders to acid suppression. In any FD trial it would be interesting to know how many patients were previous responders to PPI. On the LDQ, patients needed to have a score ⩾9 to be eligible, and the average score at entry was 13–14, indicating that patients were in the mild to moderate spectrum of disease.

In the two phase III studies, the two primary outcome measures were the GPA as described above and two questions of the LDQ: the severity of pain in the upper abdomen and feeling of upper abdominal fullness. Either a 1- or a 2-point improvement on each of the two LDQ questions was used as a primary end point. Another stipulation was that if an improvement was seen for the one LDQ question, there could not be deterioration for the other. The face validity that a 1-point improvement would be clinically meaningful is questionable.

Be that as it may, neither for the GPA nor for the 1-point improvement on the LDQ questions were there significant differences in improvement between patients treated with itopride 100 mg three times daily for 8 weeks compared with placebo. The only difference for the LDQ questions that did show a significant change was a 2-point improvement in the International trial (62% vs 53%, $p = 0.04$) but not in the North American trial (47% vs 45%).

Importantly, no significant difference was found in the proportion of patients who reported complete absence of symptoms after 8 weeks of itopride treatment (16.1% vs 13.7% in the International trial and 8.9% vs 6.6% in the North American trial).

The authors do discuss potential reasons for discrepancy in the results between the phase II and III trials. In subgroup analysis, they did find that heartburn was the best predictor of treatment response, showing a 56% response rate of itopride compared with 39% for placebo, applying a 2-point improvement on the LDQ heartburn question. As mentioned, the exclusion criteria for reflux symptoms were much stricter in the phase III programme. Although it is true that, certainly, excluding all patients with any heartburn in North America and Western Europe would probably exclude 80% of potentially eligible patients, it would only seem reasonable to conduct a trial in patients with associated heartburn symptoms if it was clearly established that such patients were non-responders to PPI treatment or, alternatively, if it is known whether they did respond to acid suppression. There is then the option to make non-response to an adequate trial of PPI (standard dose once daily given for 8 weeks) an inclusion criterion. Alternatively a study could be designed in which one of the treatment arms is a PPI. However, the interpretation of the heartburn data from the phase III studies at this point can only be considered hypothesis generating and not conclusive.

In summary, unfortunately the results of itopride appear to be truly negative in patients fulfilling strict selection criteria for FD. The latter was achieved by not allowing patients to have heartburn more than once a week. Using frequency of heartburn as an entry criterion appears to be an effective study design strategy. The good news is that we know how to conduct well-designed studies evaluating FD treatment. New efforts in the future are eagerly awaited, as there is a large group of patients who currently have an unmet medical need.

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