DYSPEPSIA MANAGEMENT

H_2 receptor antagonists and prokinetics in dyspepsia: a critical review

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Gut 2002;**50**(Suppl IV):iv58–iv62

Drug treatment of patients with functional dyspepsia is controversial but H_2 receptor antagonists have been the mainstay of treatment. For patients with symptoms suggestive of dysmotility, prokinetics such as cisapride have been used. A large number of clinical trials have been unable to produce definite answers as to whether any of these treatment modalities are truly efficacious. This is partly due to the fact that the methodology and reporting of the majority of trials evaluating the symptomatic effects of H_2 receptor antagonists and cisapride are severely flawed. Based on the current literature, H_2 receptor antagonists may possibly have a therapeutic gain of approximately 20% over placebo. Evaluating the therapeutic gain of cisapride is more difficult but meta-analyses indicate a somewhat larger effect.

SUMMARY

Drug treatment of patients with functional dyspepsia has been a matter of controversy for decades. The choice of therapy has been much influenced by the resemblance in clinical presentation to peptic ulcer disease, and H_2 receptor antagonists have therefore been the mainstay of treatment. For patients with symptoms suggestive of dysmotility, prokinetics such as cisapride have been suggested. A large number of clinical trials in this area have been unable to produce definite answers as to whether any of these treatment modalities are truly efficacious. This is partly due to problems in designing and reporting and partly due to inherent methodological difficulties in clinical trials of a vaguely defined condition such as dyspepsia, in which the only relevant outcome measure is the patient's "gut feeling".

INTRODUCTION

This review focuses on H_2 receptor antagonists and prokinetics. Only cisapride studies were included even though a number of trials have been reported evaluating domperidone. The majority of these studies were published in the 1970s and the last trial was published more than 10 years ago.[1] Sample sizes in the domperidone studies were small and the methodology and reporting of these trials were severely inadequate.[2 3] Furthermore, most clinicians today would prefer cisapride over domperidone if a prokinetic is prescribed.

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Only trials published as a full article in English or with an abstract and tabulated results in English were included. Trials reported only in abstract form and unpublished trials were not considered. Even though unpublished data could be very useful these were not sought. However, for a complete review and meta-analysis using the Cochrane criteria, it would be essential to include data from unpublished studies because publication bias makes it likely that many of these trials showed no benefit of the active drug over placebo.

Trials that focused mainly on surrogate parameters, such as histological signs of gastritis or scintigraphic signs of gastric emptying, without a symptom evaluation, were not considered.

METHODOLOGICAL PROBLEMS

Inclusion criteria

Functional dyspepsia, or non-ulcer dyspepsia, is a diagnosis of exclusion, based on dyspeptic symptoms in the absence of structural abnormalities on endoscopy. To what extent other abnormalities have been excluded by additional testing, for instance ultrasonography or oesophageal pH monitoring, is very variable. Consequently, most trials have included patients with a heterogeneous pathophysiology, and some studies, particularly those evaluating cisapride, have included patients with mild oesophagitis,[4–7] previous peptic ulceration,[7–10] and even patients with a previous vagotomy.[8 11]

The broad and non-specific definitions of dyspepsia that were used until the Rome definition was agreed upon in 1991[12] have complicated the selection of patients into trials. The Rome criteria explicitly recognise that epigastric pain or discomfort must be the predominant complaint in patients labelled as suffering from dyspepsia. Patients with predominant symptoms such as heartburn or acid regurgitation, suggestive of gastro-oesophageal reflux disease, should be excluded from the diagnosis of dyspepsia, even in the absence of structural abnormalities on endoscopy. This distinction was not made clear in many of the early trials and may thus complicate comparisons between studies over time because the inclusion criteria have obviously changed.

Evaluation of outcome

The placebo response is usually high in dyspepsia trials which should be taken into consideration when the outcome is evaluated, particularly for trials showing no benefit of the active drug. Placebo response rates in the studies evaluated in this review varied from 6% to 69%, and varied most in the cisapride studies (tables 1–3). These

Table 1 Randomised, double blind, parallel group trials of H_2 receptor antagonists versus placebo in dyspepsia

Reference	No of patients	Trial period (weeks)	Treatment	Inclusion criteria: dyspepsia type	Placebo response rate (%)	Estimated therapeutic gain (95% CI)	Investigators' conclusion
La Brooy *et al* 1978[13]	38	4	Cimetidine	Ulcer-like	?	?	Not effective
Mackinnon *et al* 1982[14]	21	6	Cimetidine	Dyspepsia and duodenitis	50	41 (35)	Effective
Bendtsen *et al* 1983[15]	33	6	Cimetidine	Ulcer-like	58	−15 (34)	Not effective
Kelbæk *et al* 1985[16]	50	3	Cimetidine	Epigastric pain	62	−8 (27)	Not effective
Nesland and Berstad 1985[9]	90	4	Cimetidine	Ulcer-like	30	17 (20)	Effective
Delattre *et al* 1985[17]	414	4	Cimetidine	Epigastric pain	57	20 (9)	Effective
Lance *et al* 1986[18]	60	4	Cimetidine	Epigastric pain/ ulcer-like	54	8 (25)	Not effective
Nyrén *et al* 1986[19]	105	3	Cimetidine	Ulcer-like	25	4 (17)	Not effective
Olubuyide *et al* 1986[20]	45	4	Ranitidine	?	?	?	Not effective
Saunders *et al* 1986[21]	221	6	Ranitidine	Dyspepsia	59	21 (12)	Effective
Gotthard *et al* 1988[22]	118	6	Cimetidine	Dyspepsia	38	16 (18)	Effective
Hadi 1989[23]	45	4	Ranitidine	Dyspepsia	45	55 (22)	Effective
Müller *et al* 1994[10]	509	4 (2)	Ranitidine	Dyspepsia	36	14 (9)	Effective
Singal *et al* 1989[24]	56	4	Cimetidine	Dyspepsia	40	27 (25)	Effective
Hansen *et al* 1998[25]	221	2	Nizatidine	Dyspepsia	62	−8 (14)	Not effective

CI, confidence interval.

discrepancies reflect the different ways of defining a response, differences among study populations, and various methodological technicalities, such as the exclusion of placebo responders during a placebo run-in phase.

One of the most troublesome methodological problems is the lack of validated outcome measures. The average dyspeptic patient complains of at least three different dyspeptic symptoms apart from epigastric pain or discomfort.[44] As a consequence, multiple testing of effects on a number of different symptoms may lead to the false conclusion that the active drug is superior to placebo.[45] Global assessments offer more valid outcome measures.[46] Furthermore, dyspeptic symptoms are not stable over time,[47] and this creates specific problems for the crossover designs used in many trials evaluating cisapride.

Selection bias

Study populations have usually been recruited from the small proportion of dyspeptic patients referred for endoscopy and from highly specialised referral centres with a specific interest in dyspepsia. Patients with dyspeptic symptoms who obtain relief from over the counter medicine and patients who respond favourably to empirical drug treatment in primary care are less likely to be referred for endoscopy or to referral centres and thus recruited to clinical trials.[48] Accordingly, there is a risk that the study populations in these trials constitute non-responders to drug treatment. As a consequence, the implications of such drug trials are uncertain or unknown for the vast majority of dyspeptic patients who are managed in primary care settings. Only six of the 45 studies evaluated in this review recruited patients directly from the primary care setting.

Heterogeneity

Given the heterogeneity of dyspepsia, it is unlikely that a single drug will work for all patients. The placebo response is high and some patients may even deteriorate while receiving active drug treatment. As a consequence, parallel group studies may mask individual responders to treatment. This problem has been addressed by special study designs, such as the single subject trial designs, multiple crossover designs,[49–54] and by post hoc analysis of patient characteristics in groups of responders.

Dyspeptic symptoms are usually chronic or recurrent. It is thus a surprise that in the majority of trials patients were treated for six weeks or less, and no study included long term follow up after cessation of treatment.

H_2 RECEPTOR ANTAGONISTS IN DYSPEPSIA

Twenty two studies comparing a H_2 receptor antagonist with placebo were evaluated.

Parallel group studies

Fifteen trials used a parallel group design.[9 10 13–25] Ten studies evaluated cimetidine,[9 13–19 22 24] four studies ranitidine,[10 20 21 23] and one study nizatidine.[25]

A summary of the trial design, number of randomised patients, inclusion criteria, and outcome measures is reported in table 1.

Inclusion criteria

Epigastric pain or ulcer-like symptoms were the main inclusion criteria in seven of the studies (table 1).[9 13 15–19] In the remaining studies, the dyspepsia type was not specified or a mixture of different dyspeptic symptoms was allowed.

Outcome

In seven studies, the authors claimed a statistically significant benefit of the active drug over placebo.[10 14 17 21–24] However, in three studies,[14 22 24] a reported significant effect of the active drug could not be confirmed after a simple re-analysis of the raw data presented in the tables in the articles. Thus only four studies[10 17 21 23] showed a significant effect of the H_2 receptor antagonist over placebo.

Table 1 summarises the estimated therapeutic gain (difference in success rates, as defined by the individual trial, between placebo and active drug and the related 95% confidence interval) for 12 of the studies. In the remaining two studies, the reported data did not allow an estimate of therapeutic gain. Placebo response rates in the three large scale studies reporting a significant effect of the H_2 receptor antagonist were 36%,[10] 57%,[17] and 59%,[21] and the therapeutic gains 14%, 20%, and 21%, respectively. In the study by Müller *et al*, at least one fifth of the included patients had a positive history of peptic ulcer disease or gastro-oesophageal reflux disease, which may have contributed to the significant effect of ranitidine over placebo in patients with acid related symptoms.[10] The most recent study, which recruited unselected dyspeptic patients directly from primary care, was unable to detect any benefit of nizatidine over placebo.[25]

Crossover studies

Seven studies have used crossover or multiple crossover designs. The study by Talley *et al* was unable to show any benefit in the global assessment of symptoms.[55] The other six

Table 2 Randomised, double blind, parallel group trials of cisapride versus placebo in dyspepsia

Reference	No of patients	Trial period (weeks)	Inclusion criteria: dyspepsia type	Placebo response rate (%)	Estimated therapeutic gain (95% CI)	Investigators' conclusion
Coutant *et al* 1987[5]	32	4	Dysmotility-like	36	44 (41)	Effective
Rösch 1987[26]	118	4	Dyspepsia	31	50 (16)	Effective
De Nutte *et al* 1989[11]	32	4	Epigastric pain	50	32 (21)	Effective
Jian *et al* 1989[27]	28	6	Dysmotility-like	?	?	Not effective
Agorastos *et al* 1991[6]	36	4	Dysmotility-like	?	?	Effective
Hausken and Berstad 1992[28]	120	4	Epigastric pain/discomfort	40	10 (18)	Not effective
Van Outryve *et al* 1993[8]	53	2	Epigastric pain/burning	22	43 (24)	Effective
Chung 1993[29]	29	4	Dysmotility-like	20	51 (31)	Effective
Frazzoni *et al* 1993[30]	28	4	Dyspepsia	69	21 (27)	Not effective
Wood *et al* 1993[31]	11	4	Epigastric pain/discomfort	?	?	Not effective
Kellow *et al* 1995[32]	61	4	Dyspepsia	66	−8 (23)	Not effective
Al-Quorain *et al* 1995[33]	89	4	Dyspepsia	27	60 (16)	Effective
de Groot and de Both 1997[34]	113	4	Dyspepsia	44	19 (19)	Not effective
Champion *et al* 1997[35]	123	6	Epigastric pain	33	12 (20)	Not effective
Yeoh *et al* 1997[36]	76	4	Epigastric pain/discomfort	50	5 (21)	Not effective
Hansen *et al* 1998[25]	221	2	Dyspepsia	62	0 (14)	Not effective

CI , confidence interval.

Table 3 Randomised, double blind, crossover trials of cisapride versus placebo in dyspepsia

Reference	No of patients	Trial period (weeks)	Inclusion criteria: dyspepsia type	Placebo response rate (%)	Cisapride response rate (%)	Investigators' conclusion	Comments
Milo 1984[37]	16	2×3	Dyspepsia/reflux	6	75	Effective	No washout period
Creytens 1984[38]	16	2×3	Dysmotility/reflux	56	94	Effective	No washout period
Francois and De Nutte 1987[39]	34	2×3	Epigastric pain/burning	41	82	Effective	Washout period. Period effect found
Deruyttere *et al* 1987[7]	56	2×3	Dysmotility/reflux	55	75	Effective	No washout period. Period effect found
Deruyttere *et al* 1987[40]	128	2×3	Dysmotility/reflux	43	77	Effective	No washout period. Period effect found. Possible double publication
Goethals and van de Mierop 1987[41]	24	2×4	Dysmotility/reflux	29	63	Effective	No washout period. Period effect found
Hannon 1987[4]	22	2×3	Dysmotility/reflux	27	64	Effective	No washout period
Van Ganse and Reyntjens 1987[42]	8	2×1	Dysmotility/reflux	13	88	Effective	No washout period
Corinaldesi *et al* 1987[43]	12	2×2	Dysmotility	?	?	Not effective	No washout period

studies were single subject trials using a multiple crossover design to identify individual responders to treatment.[49–54] All of these studies claimed that a small proportion of patients, typically 10–20%, obtained significantly better symptom relief during the periods on the H_2 receptor antagonists compared with periods on placebo. A therapeutic gain cannot be estimated from these study designs. Patients who responded to H_2 receptor antagonists were characterised by heartburn or other features suggestive of gastro-oesophageal reflux disease as well as dyspepsia.

Meta-analyses

Two meta-analyses have tried to summarise the overall symptomatic effects of H_2 receptor antagonists in dyspepsia. Based on six trials, Dobrilla *et al* estimated a significant therapeutic gain over placebo in the order of 20%.[56] This conclusion was confirmed in a more recent analysis by Finney and colleagues.[57] None of the meta-analyses included unpublished data however.

CISAPRIDE IN DYSPEPSIA

Inclusion criteria

Twenty five cisapride studies were reviewed.[4–8 11 25–43]

In seven of the 25 studies, the main entry criteria were epigastric pain or discomfort, or so-called ulcer-like dyspepsia (tables 2 and 3).[8 11 28 31 35 36 39] In the remaining 18 studies, patients were troubled by symptoms suggestive of dysmotility or a mixture of dyspeptic symptoms, including symptoms associated with gastro-oesophageal reflux disease.

Parallel group studies

A total of 16 studies compared cisapride with placebo in a parallel group design.[5 6 8 11 25–36] These are summarised in table 2. Some of the early studies randomised rather few patients, they often claimed a positive response, and two of these studies allowed patients with mild oesophagitis.[5 6] Seven of the 16 studies reported a significant improvement with cisapride compared with placebo,[5 6 8 11 26 29 33] but five of these trials randomised patients with dysmotility-like or mixed dyspeptic symptoms.[5 6 26 29 33]

Five studies randomised more than 100 patients.[25 26 28 34 35] Of these five studies, only the early study by Rösch showed a significant improvement with cisapride.[26] The other four, all published within the last seven years, were negative.

In 13 of the studies, a therapeutic gain could be estimated.[5 8 11 25 26 28–30 32–36] The values are summarised in table 2 and varied from −8% to +60%.

The majority of studies recruited patients in secondary or even tertiary centres, evaluating only highly selected patients. Only three studies recruited patients directly from primary care and all were negative.[25 31 34]

Crossover studies

A number of crossover studies have been reported. It is particularly difficult to review this part of the literature and the majority of these trials were hampered by imperfect methodology and poor reporting.

The main findings from nine trials are summarised in table 3.[4 7 37–43] Seven of the trials had randomised fewer than 40 patients.[4 37–43] The majority of the trials claimed a significant effect of the active drug.[4 7 37–42] However, none of the studies complied with common standards concerning design, analysis, and reporting of crossover trials. For instance, a washout period to exclude period effects before a shift to the alternate treatment was seldom included. Furthermore, the results reported by Deruyttere *et al* may represent double publication, summarising the results from three previous publications even though this was not specifically stated in the paper.[40]

Meta-analyses

Three meta-analyses have evaluated the effects of cisapride. The analysis by Dobrilla *et al* based on seven studies concluded that cisapride had a therapeutic gain of 39%.[56] That conclusion was based on a total of only 275 patients from six crossover studies and just one parallel group study.

In the meta analysis by Finney *et al*, eight studies were included.[57] Based on 415 patients from three crossover trials and five parallel group studies, an overall therapeutic gain of 36% was found. However, this meta-analysis did not include the recent negative large scale studies by de Groot and de Both,[34] Champion and colleagues,[35] Yeoh and colleagues,[36] and Hansen and colleagues.[25] These four studies alone had more patients randomised compared with the eight studies included in the meta-analysis.

Using a somewhat different design, Veldhuyzen van Zanten *et al* have published a meta-analysis including 18 studies.[58] They found cisapride to be efficacious based on global assessment rated by the investigator. However, individual symptoms such as epigastric pain, abdominal distension, and nausea were not improved. Furthermore, none of these meta-analyses included unpublished data.

CONCLUSION

The methodology and reporting of the majority of trials evaluating the symptomatic effects of H_2 receptor antagonists and cisapride are severely flawed and the published conclusions should be evaluated very carefully. Based on the current literature, H_2 receptor antagonists may possibly have a therapeutic gain of approximately 20% over placebo. Patients with heartburn and other symptoms suggestive of gastro-oesophageal reflux disease are most likely to respond. Evaluating the therapeutic gain of cisapride is more difficult but meta-analyses indicate a somewhat larger effect. This conclusion however is based mainly on highly selected patients who often have symptoms suggestive of dysmotility rather than epigastric pain, and whether this effect translates back to the vast majority of dyspeptic patients, who are managed in primary care, is very doubtful.

We need long term studies of better quality in unselected patients in primary care before we can draw any firm conclusions about the effects of these drugs in the target population. Head to head comparisons between different treatment modalities are also needed.

Conflict of interest: This symposium was sponsored by AstraZeneca, makers of omeprazole. The author of this paper has received sponsorship for travel and an honorarium from AstraZeneca.

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