Loxiglumide, a CCK-A Antagonist, in Irritable Bowel Syndrome

A Pilot Multicenter Clinical Study

P. A. CANN,[a] L. C. ROVATI,[b,f] H. L. SMART,[c] R. C. SPILLER,[d] AND P. J. WHORWELL[e]

[a]*Middlesbrough General Hospital*
Middlesbrough, UK

[b]*Department of Clinical Pharmacology*
Rotta Research Laboratorium
20052 Monza, Italy

[c]*Royal Hallamshire Hospital*
University of Sheffield
Sheffield, UK

[d]*Queen's Medical Centre*
University of Nottingham
Nottingham, UK

[e]*University Hospital of South Manchester*
Manchester, UK

Cholecystokinin (CCK) is a neurohormonal peptide that is involved in the regulation of several digestive functions, contributing to the control of motility and secretions at different organ levels. Evidence indicates that CCK might be involved in the pathogenesis of irritable bowel syndrome (IBS).[1] Loxiglumide (CR 1505, that is, D,L-4-[3,5-dichlorobenzoylamino]-5-[*N*-3-methoxy-propil-pentylamino]-5-oxo-pentanoic acid) is a potent, selective, competitive, and orally bioavailable CCK_A receptor antagonist,[2,3] and it is the most widely used in physiological and therapeutic human studies.[4,5] Interestingly, loxiglumide appeared to accelerate colonic transit in healthy volunteers and chronic constipated elderly subjects[6,7] and to regulate regional colonic transit in IBS patients with different bowel habit patterns.[8] CCK_A antagonists have been proposed as potential candidates for drug treatment of IBS,[9] and we were therefore interested in testing the efficacy of loxiglumide on IBS symptoms in a pilot dose-response study, using doses only minimally affecting other gastrointestinal physiological functions such as gallbladder contraction.[10]

PATIENTS AND METHODS

Patients who, in the absence of organic digestive diseases, complained of abdominal pain and a disturbance of bowel habit for at least 6 months and on at least 3 days a week (to be confirmed by diary cards during a 2-week baseline period) were assigned to oral treatment with either placebo or loxiglumide 200 or 400 mg three

[f]Address for correspondence: Lucio C. Rovati, MD, Department of Clinical Pharmacology, Rotta Research Laboratorium S.p.A., Via Valosa di Sopra 7/9, 20052 Monza (MI), Italy.

times daily for 8 weeks, according to a randomized, double-blind, parallel-group design. Seventy-two patients satisfied the criteria for evaluation. Fourteen symptoms, mainly related to abdominal pain/discomfort and bowel habits, were each rated on a 100-mm VAS and on a 0–4 scale. Overall efficacy assessment by either patients or physicians were also recorded. Based on a forecasted placebo response rate of 40% and at least on a 15–20% superiority in one of the loxiglumide groups, ~100 patients per group would be necessary to show statistical significance (with alfa = 0.05 and beta = 0.2). This pilot study was designed to confirm this hypothesis and to be tested in larger trials. "Therapeutic responders" were patients with a positive overall efficacy assessment by patients themselves or physician and a decrease ≥25% (compared to baseline) in an overall symptom score defined by the sum of VAS of the considered symptoms.

RESULTS AND CONCLUSIONS

Oral loxiglumide 400 mg three times daily for 8 weeks induced a significant improvement in IBS symptoms (including abdominal pain, distention, and change in bowel habit) compared to placebo and to a lower dose of 200 mg three times daily. This effect was more evident in constipation-predominant patients (C-IBS), and indeed abdominal pain and distention and constipation showed a ~50% improvement rate. The effects of loxiglumide on diarrhea-predominant IBS patients (D-IBS) were of similar magnitude (including diarrhea itself), but the sample size was small and placebo induced a similarly high response. Overall (sum of all symptoms in all patient subgroups), loxiglumide 400 induced a 63% ($n = 24$) responder rate, loxiglumide 200 57% ($n = 23$), and placebo 48% ($n = 25$). Loxiglumide superiority was confirmed, to a similar extent, by both the patients' and physicians' overall assessment, but the patients gave both doses of loxiglumide an equal score. Both patient and physician differentiated the active drug from placebo in the C-IBS subgroup, whereas the D-IBS subgroup was very sensitive also to the placebo effect. The three treatments were equally well tolerated. In conclusion, the CCK_A antagonist loxiglumide is a promising drug in the treatment of IBS according to the results of this first pilot study. Further larger trials are necessary to confirm these results and the possible role of CCK in the pathophysiology of IBS.

REFERENCES

1. Harvey, R. F. & A. E. Read. 1973. The Lancet I: 1.
2. Setnikar, I., M. Bani, R. Cereda, R. Chistè, F. Makovec, M. A. Pacini, L. Revel, L. C. Rovati & L. A. Rovati. 1987. Arzneim.-Forsch. 37: 703.
3. Setnikar, I., M. Bani, R. Cereda, R. Chistè, F. Makovec, M. A. Pacini & L. Revel. 1987. Arzneim.-Forsch. 37: 1168.
4. Rovati, L. C. 1991. Int. J. Pancreatol. 8: 215.
5. Adler, G. & C. Beglinger, eds. 1991. Springer-Verlag. Berlin-Heidelberg.
6. Meyer, B. M., B. A. Werth, C. Beglinger, P. Hildebrand, J. M. B. J. Jansen, D. Zach, L. C. Rovati & G. A. Stalder. 1989. Lancet II: 12.
7. Meier, R., C. Beglinger, M. Thumshirn, B. Meyer, L. C. Rovati, G. Giacovelli, M. D'Amato & K. Gyr. 1993. J. Gastrointest. Mot. 5: 129.
8. Barrow, L., P. E. Blackshaw, C. G. Wilson, L. C. Rovati & R. C. Spiller. 1992. J. Gastrointest. Mot. 4: 207.
9. Read, N. W. 1991. *In* Cholecystokinin Antagonists in Gastroenterology: Basic and Clinical Status. :214. Springer-Verlag. Berlin-Heidelberg.
10. Malesci, A., C. DeFazio, S. Festorazzi, C. Bonato, A. Valentini, M. Tacconi, M. Bekkering, G. Giacovelli, M. D'Amato & L. C. Rovati. 1992. Arzneim.-Forsch.