

EFFECTS OF CISAPRIDE ON CONSTIPATION DUE TO SPINAL CORD INJURY: REPORT OF FIVE WARFARE SPINAL CORD INJURED PATIENTS

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ABSTRACT

Five warfare spinal cord injured patients with intractable constipation are described. Treatment with cisapride (4×10 mg daily) was undertaken. The agent cisapride significantly reduced the oral-anal transit time from 25.2 days to 14.4 days. It also improved other subjective complaints of these patients markedly. No side effects were seen during the trial.

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INTRODUCTION

Severe spinal cord injury results in motor paralysis which is later complicated by bladder and bowel problems.¹ The most common bowel problem in the later phase is fecal impaction,² and intractable constipation.³ Cholinergic agents (like bethanecol) and prokinetic benzamides (like methoclopramide) have been in an attempt to overcome the lack of parasympathetic cholinergic stimulation but they are disappointing because of their side effects. Recently, cisapride has been described as a non-cholinergic gastrointestinal motor stimulant, supposedly acting through increased release of acetylcholine in the intramural plexuses.⁴ Its prokinetic effects have been demonstrated in patients with motility disorders of upper gastro-intestinal tract.^{4,5,13} The present study investigates the effects of cisapride on constipation and oral-anal transit time (OATT) in spinal injured subjects. The study was part of a wider project of which ethical permission was granted by Center of Research and Treatment on Warfare Spinal Cord Injured of Khorasan province.

PATIENTS AND METHODS

Five victims of the Iran-Iraq war with complete traumatic spinal cord injury in chronic stage of their disease were

studied. Patients were all male with mean age of 28.1 years (range 20-42 years). The level of cord injury varied from C4 to L2. The mean time since injury was 5.2 years (range 2-8 years). All patients gave informed consent and were investigated while in the Center of Research and Treatment on the Warfare Spinal Cord Injured of Khorasan.

When patients entered the trial, the extent of their constipation was determined by first establishing their intestinal transit times. For this purpose oral-anal transit time (OATT) was estimated using small radiopaque pellets as a marker and X-raying of the stools.⁷ This allows a reasonable measure of transit time and avoids unnecessary exposure of the subject to X-rays. Although colonic transit time (CTT) which is a better reflexion of the degree of constipation was not measured in this study, the fact that oral-caecal transit time (OCTT) which could be estimated by using the oral lactulose and expired breath hydrogen method⁷ is very short (only few hours) and is fairly constant even in patients with spinal cord injury,⁸ we assume that OATT is as accurate as CTT for evaluation of constipation in these patients. The method of stool collection was by manual rectal evacuation with the occasional spontaneous evacuation.

A digital rectal examination was performed each morning after breakfast and rectal contents were evacuated into the collection bag. Stool collection was continued until each transit time estimation was complete. Then the

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estimation was repeated while patients were given cisapride (Janssen Pharmaceutical, Ltd) 4 × 10 mg daily and cisapride was continued until each transit time was complete.

In addition to constipation all patients had chronic abdominal complaints such as abdominal pain, nausea, bloating, and flatulent dyspepsia. They underwent a thorough search for an infectious or anatomic source for these symptoms before trial. Symptoms were rated as none, mild, moderate or severe and scored with the numbers 0, 1, 2, 3, respectively. This standardized rating system was used for all symptoms. A total symptoms score was computed by adding the sum of numbers for each symptom. For each patient the score of abdominal pain, nausea, bloating, and flatulent dyspepsia were added together to obtain the total symptom score. Total symptom score was measured in all patients before trial (baseline) and five days after taking cisapride. Efficacy of cisapride to improve these symptoms was also determined.

RESULTS

The results of OATT are given in Table I and Fig. 1. Average OATT was reduced from 604 hours to 345 hours and achieved statistical significance, with $P < 0.005$. Symptoms improved significantly ($P < 0.05$) from the baseline symptoms (median score 8) to the 5th day of trial (median score 6). Score for individual symptoms (baseline and at 5th day) are given in Table II. Significant improvement was noted for abdominal pain, bloating, and flatulent dyspepsia.

DISCUSSION

Intractable constipation and fecal impaction are the most common complications of chronic spinal cord injury.² The constipation in spinal injury subjects may be due to interruption, at the spinal level, of the extrinsic nerve supply to the distal nerve plexus which has a degree of spontaneous activity. This myenteric plexus can also be stimulated by the extrinsic nerve supply of the colon. As neuroprosthetic stimulation to increase the activity of the colon is not yet as appropriate as its use for bladder stimulation, a suitable pharmacological preparation capable of stimulating intestinal motility would have more immediate application. The agent cisapride is a synthetic substituted benzamide which has been shown to have a potent prokinetic affect on the smooth muscles of gastrointestinal tract,⁴ probably by releasing acetylcholine at the myenteric plexus.⁹ The effects of cisapride on the motility of the upper digestive tract closely resemble those of methochloramide and domperidone. However, unlike these drugs, it also increases colonic motility and can cause

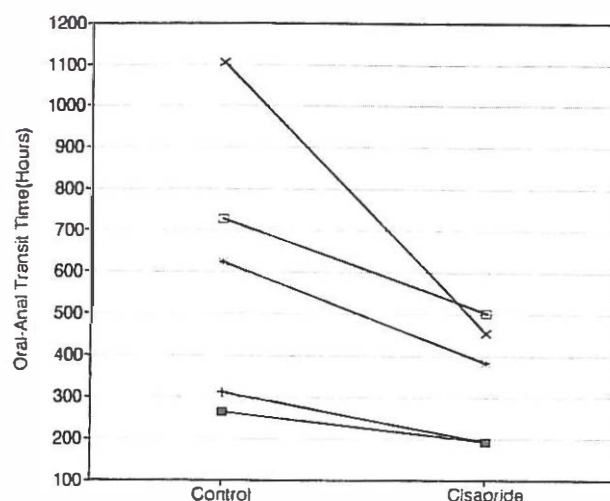


Fig. 1. Oral transit time measured in hours. The transit time before cisapride is given under "Control" while transit time with the effect of the drug is given under "Cisapride".

Table I. Results of OATT. Those measured before cisapride was taken orally are in the column headed "Control" and those recorded with cisapride are in the column termed "Cisapride"

Patients	Control	Cisapride
1	26 days	16 days
2	46 days	19 days
3	13 days	8 days
4	11 days	8 days
5	30 days	21 days

Table II. Change in Median Symptom Scores from baseline to five days after treatment

Symptom	Baseline	5 days cisapride	P
Abdominal pain	3	1	0.05
Nausea	1	1	NS
Bloating	4	1	<0.05
Flatulent dyspepsia	3	1	0.05

diarrhea.¹⁰

Cisapride appears to be devoid of dopaminergic blocking activity and it does not influence the concentration of prolactin in plasma or cause extrapyramidal symptoms. Thus far the efficacy of the drug in the treatment of disorders of gastric hypomotility appears to equal those of methochloramide and domperidone without the side effects that result from dopaminergic blockage.¹¹ However, its effect on colonic dysfunction with fecal stasis has been reported infrequently.¹² The present study shows that in

spinal injured subjects, cisapride significantly reduces intestinal transit time and improves chronic gastrointestinal problems in the majority of cases.

The beneficial effect of cisapride in our study does not appear to be a placebo effect, because our patients have used many drugs for years. There appeared to be no adverse effects on heart rate or blood pressure. No side effects on parameters of complete blood count, urea, electrolytes and liver function tests were noted. Regarding the long-term effects of cisapride, there are to date several subjects (not in our study) who have taken the drug in excess of one year.^{13,14} The beneficial effect on colonic function and upper motility disorders has remained. No deleterious long-term effects of oral cisapride have been noted.

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