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The effects of 4 weeks treatment with cisapride on cystometric parameters in spinal cord injury patients. A double-blind, placebo controlled study

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A group of 21 complete spinal cord injury patients, beyond the phase of spinal shock, were given a treatment of cisapride at random, 10 mg four times a day for 4 weeks. Cystometry was performed first before the start and during the following 4 weeks. No statistically significant difference could be found in the urodynamic parameters between the two groups at the first cystometry. No statistically significant change of the urodynamic parameters could be demonstrated with the treatment, although a non-statistically significant bladder stimulating effect was present in a majority of the patients in the cisapride group.

Keywords: paraplegia; cystometry; cisapride; neuropathic bladder

Introduction

Cisapride is a prokinetic drug which facilitates acetylcholine delivery from postganglionic nerve ends in the plexus myentericus of the smooth muscles of the gastrointestinal tract. It stimulates the motility of the smooth muscle lining the oesophagus, stomach, small intestine, and colon, and increases the tone of the gut sphincters *in vitro* and *in vivo*.[1] Activity in the treatment of constipation in paraplegic people has been noted.[2] Some reports have described the effects of cisapride on urodynamic function. We evaluated several cystometric parameters in spinal cord injury (SCI) patients after 4 weeks of cisapride intake in a double-blind, placebo controlled study.

Patients and methods

Twenty two inpatients with a clinically complete SCI are included in the study. One was lost early in the study during treatment follow-up, which left 21 patients for evaluation. They were four female and 17 male patients, mean age 32 years old (from 17 to 59 years old). Their mean weight was 67.3 kg (from 45 to 86 kg).

The level of the SCI, the interval between the SCI and the date the study started are given in Table 1. In 18 patients, the SCI was caused by trauma (eight road accidents, 10 from other forms of trauma). In three patients, there was a medical cause (intervertebral disc one, spondylodiscitis one, tumour one).

All patients were out of spinal shock for more than 1.5 months before entering the study. In three patients, the anorectal and bulbocavernosus reflexes were negative. In the other patients these reflexes were easily demonstrated clinically.

Inclusion was done at random. Exclusion criteria were pregnancy; lactation or the possibility of becoming pregnant during the study; inability to participate in the two cystometric investigations; some other pathology which could influence the normal study period, such as severe cardiovascular or pulmonary problems and renal insufficiency; surgery on the lower urinary tract which could influence cystometric behaviour; the intake of gastrokinetic, antiemetic drugs, calcium-entry blockers, antispasmodics, anticholinergic or cholinergic drugs; urinary tract infection at the moment of cystometry.

The study was conducted as a double-blind placebo controlled, parallel group investigation. Patients were allocated at random to the group receiving cisapride, or the group receiving placebo for 4 weeks.

Table 1 Level of spinal cord injury (SCI) and interval between SCI and the date the study was started. ( ) = patient left study early

Cisapride			*Placebo*		
Patient	*Level SCI*	*Interval*	*Patient*	*Level SCI*	*Interval*
3	T6	12	1	T8	6
4	C7	11	2	T6	2
7	L1	1	5	L1	5
(8	T8	3)	6	C6	4
9	C8	2	10	T12	6
11	T4	181	12	T12	6
14	T9	12	13	C8	3
15	C2	11	16	T5	4
17	C7	50	19	T12	3
18	C4	10	20	C6	6
21	T9	10			
22	T10	5			

Identical tablets with 10 mg cisapride or placebo were used, one tablet being taken four times a day 15 min before each meal and before going to sleep. Tablets were delivered to the patients by the ward nurse.

Cystometry was performed before the start of medication intake and during the following 4 weeks. Water filling cystometry was done, the bladder being filled at a rate of 30 ml min^{-1} through an 8 Fr catheter introduced transurethrally. A solution of 200 ml Urographine 76% (Shering, USA) in 700 ml sterile water at room temperature was injected by a continuous flow pump (JTL RM 302, France). Patients were in the supine position on a Hydrajust radiological table (Sybron Liebel-Flarsheim, USA). The intravesical pressure was measured by a microtransducer located on a Gaeltec 8 Fr. catheter (Gaeltec, Scotland) introduced through the urethra. Another microtip transducer protected inside a waterfilled balloon (10 ml) and placed in the rectum was used to measure the intra-abdominal pressure. A six channel DISA urovideosystem (Disa-Dantec, Denmark) was used with automatic subtraction of the intravesical and the intra-abdominal pressure to give the detrusor pressure. The following parameters were evaluated: maximum cystometric capacity; volume at the first sensation of filling; volume at the sensation to void; maximum detrusor pressure; compliance (calculated on the maximum bladder filling); bladder capacity at the first involuntary (hyperreflexic) detrusor contraction; and the residual urine.

Methods, definitions and units conformed to the standards recommended by the International Continence Society.[3] Statistical analysis was performed by the Wilcoxon matched pairs signed-rank test for comparing the data before and after medication intake. To compare the urodynamic data before the start of the study between the cisapride and the placebo group, the Mann–Whitney U-test was used. The study was approved by the local ethical committee.

Results

All 21 patients completed the study as planned. Patient compliance was easily controlled in inpatients.

There was no significant difference in the urodynamic parameters before the start of the study between both groups.

The urodynamic data at the first and the second cystometry are given in Table 2. No statistically significant difference was found in any of the parameters studied in either the cisapride or the placebo group.

Sensation of filling (both the first sensation of filling and the sensation to void) was absent in 10 patients on cisapride and in three patients on placebo at both cystometric investigations. In another four patients on placebo the presence or absence of sensation varied between the two cystometric investigations. Therefore, the data are insufficiently available for the evaluation of the influence of the medication/placebo on these parameters.

Discussion

A possible influence of cisapride intake on vesicourethral function in SCI patients has been documented by a few authors. Hanson and Soler (1989) observed a reduction of the postmicturition residual urine in patients with a neurological bladder disturbance.[4]

Binnie *et al* described the same observation in a study on 10 SCI patients treated with cisapride 10 mg i.v. and, after an interval of 48 h, with 10 mg p.o. three

Table 2 Urodynamic data in patients before and after 4 weeks' intake of cisapride or placebo

	Cisapride			*Placebo*		
	Mean	*SD*	*(Min–max)*	*Mean*	*SD*	*(Min–max)*
Maximum cystometric capacity (ml)						
Pre	322	138	(150–600)	413	195	(100–600)
Post	331	156	(164–700)	406	135	(200–600)
Maximum detrusor pressure (cm H_20)						
Pre	41	23	(10–80)	56	21	(22–76)
Post	60	37	(10–120)	48	22	(21–72)
Compliance (ml cm H_20^{-1})						
Pre	30	31.5	(6–100)	26	16	(10–60)
Post	24	12	(7.5–41)	33	18	(10–66)
Capacity at first hyperreflexic detrusor contraction (ml)						
Pre	207.5	114	(100–360)	164	49	(100–205)
Post	152.5	83	(20–250)	202	83	(140–320)
Residual urine (ml)						
Pre	267	187	(65–600)	242	244	(40–600)
Post	230	220	(20–700)	318	276	(10–600)

SD = Standard deviation
Wilcoxon matched pairs signed rank test gives no significant difference in all comparisons

times a day for a few days.[2] They found a reduction of the residual urine volume from 51.5 ml (SD 16.7 ml) to 27.7 ml (SD 8.4 ml). In one patient, who normally emptied his bladder by suprapubic tapping, the unwanted side effect of acute retention of urine was noted on the morning after the abrupt cessation of oral cisapride. This resolved after 1 day of intermittent catheterisation. The authors also mentioned the increased frequency of micturition in three subjects with an incomplete SCI being treated with cisapride for colonic transit problems. This increased frequency was troublesome in one female subject and was corrected by reducing the dosage of cisapride to 10 mg twice a day.

De Groat and de Pagter[5] treated two patients with intractable constipation and an atonic bladder due to a partial spinal cord lesion and sacral nerve lesion.[5] In one patient, cystometry showed that with cisapride 4×10 mg daily, earlier and more spontaneous contractions of the bladder occurred. This resulted in more efficient bladder emptying and the absence of frequent bladder infection.

Etienne *et al* treated one 57-year-old paraplegic patient with a SCI at T12 level and a neuropathic bladder. Under cisapride urinary residual was lowered substantially. The effect was maintained during a follow-up of 18 months.[6]

Carone *et al* treated 15 patients with a complete traumatic SCI for 3 days with cisapride 10 mg. Cystometry was performed before and after medication intake. In all patients, a significant change in detrusor activity was noticed. In those with hyperreflexic bladders earlier and higher amplitude reflex contractions were seen.

Hypoactive bladders had a significant reduced compliance at 400 ml filling. No definite modifications were observed in maximal urethral closure pressure, nor functional alterations in the striated sphincter.[7]

In our paper, a double-blind placebo controlled study is presented with urodynamic investigation done before and after 4 weeks of treatment. Parameters related to bladder filling (maximum cystometric capacity, compliance), to the detrusor contraction (maximum detrusor pressure, capacity at first involuntary contraction) as well as residual urine volume showed no significant difference before and after treatment either in the cisapride or in the placebo group. If we look in detail into each individual parameter, some influence of cisapride could possibly exist. In the cisapride group, maximum detrusor pressure increases under treatment in five/nine patients, compliance lowers in six/ten patients. Volume at first involuntary contraction is lower in five/eight patients and residual urine is less in six/nine patients on cisapride. These observations however cannot be made in the placebo group. However, statistically the difference pre and post treatment is not significant.

We conclude that in our study the clear influence of cisapride intake 10 mg p.o. four times a day on urodynamic function in SCI patients, as is described in a small number of patients by some authors, cannot be found. The results were not significantly different for cisapride and placebo intake, although in a majority of patients on cisapride some bladder stimulating effect appeared to be possible.

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