



위장관 운동 촉진제

- 우리나라에서 기능성 위장관 질환에 사용되고 있는 약물에 대한 문헌 검토


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Definition of Prokinetics



- Drugs that stimulate gastrointestinal smooth muscle contractions
- Leading to enhanced gastrointestinal motility and transit

Tack J, et al. Curr Opin Pharmacol 2008;8:690-6

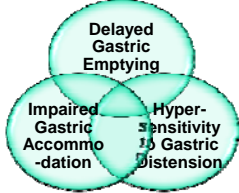


Role of Prokinetics

- GERD
 - Delayed gastric emptying
 - Persistent GERD symptoms despite the use of PPI
- Functional dyspepsia
 - Delayed gastric emptying
- Irritable bowel syndrome
 - Constipation-dominant





Prokinetics in Functional Dyspepsia



- Heterogeneous underlying pathophysiology
 - Delayed gastric emptying: 40%
- Identifying subgroup based on symptom cluster
 - Postprandial fullness, nausea, vomiting
 - Inconsistent

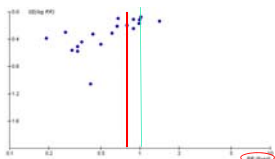
Talley NJ, et al. Am J Gastroenterol 2005;100:2324-2337




Systematic Reviews on FD

- Prokinetics are effective!!!

- 24 RCTs for meta-analysis
- Significantly more effective than placebo
 - 57% vs 47%
- Relative risk reduction: 33%
- Number needed to treat: 6



Moayyedi P, et al. Cochrane Database Syst Rev 2006;4:CD001960




Systematic Reviews on FD

- Cautions for interpretation

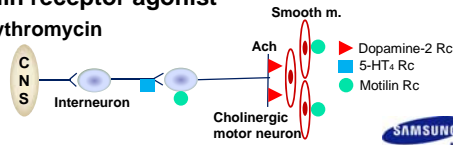
- Most studies
 - Cisapride (18 RCTs)
 - Publication bias
 - Improvement in symptoms vs Improvement in delayed gastric emptying

Moayyedi P, et al. Cochrane Database Syst Rev 2006;4:CD001960



Classification of Prokinetics

- **Dopamine₂ receptor antagonist**
 - Domperidone, metoclopramide
 - Itopride, levosulpiride, clebopride, bromopride
- **5-HT₄ receptor agonist**
 - Cisapride, tegaserod: withdrawal from market
 - Mosapride, prucalopride
- **Motilin receptor agonist**
 - erythromycin



Rationale for Blockade

- **Dopamine**
 - Potent inhibition of GI motility
 - Reducing gastric tone
 - Impairing antroduodenal coordination
 - Reducing LES tone
- **Dopamine₂ Receptor Antagonist**
 - Prokinetics
 - GERD treatment

Tack J, et al. Dig Dis 2006;24:297-307

Metoclopramide - Effective for diabetic gastroparesis

- **Mechanism**
 - Dopamine₂ receptor antagonist
 - 5-HT₄ receptor agonist: partial → Ach release
- **Mainly studied in diabetic gastroparesis**

Author/year/reference	Study design	No. of subjects	Types of patients	Dosage of metoclopramide	Length of study	Outcome results
Pariel et al. 1979 ¹⁰	Randomized, double-blind, parallel group placebo controlled	28	Diabetic gastroparesis (5) Postsurgical gastroparesis (4) Idiopathic gastroparesis (19)	10 mg QID	3 wk	Improved symptoms by 29%
Snape et al. 1982 ¹¹	Randomized, double-blind, crossover placebo controlled	10	Diabetic gastroparesis	10 mg QID	3 wk	Improved symptoms in 7 of 10 by 50% Improved gastric emptying by 31% Poor correlation between gastric emptying and symptoms
McCallan et al. 1983 ¹²	Multicenter, placebo controlled	18	Diabetic gastroparesis	10 mg QID	3 wk	Improved symptom score by 25% Improved gastric emptying by 25%

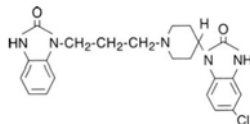
Parkman HP, et al. Gastroenterology 2004;127:1592-1622

Metoclopramide - Side effect

- Antidopaminergic action in CNS
- Long-term use
- Drowsiness, fatigue, agitation, irritability
 - 30%
- Tardive dyskinesia
 - Involuntary movements of face, tongue, or extremities
 - 1-15%
- Parkinson-like symptoms
- Hyperprolactinemia
 - Galactorrhea, gynecomastia

Domperidone - Effective for FD in meta-analysis

- 211 patients in 4 RCTs
- 10 mg tid to 10 mg qid
- 2 to 4 weeks
- Domperidone vs Placebo



Outcome	OR	95% CI	Homogeneity	
			χ^2	I^2
Global assessment rated as excellent	7.44	3.57, 15.51	2.02	0.00
Global assessment rated as ≥ good	17.38	9.16, 32.95	1.84	0.00

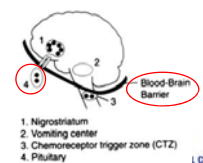
van Zanten V, et al. Am J Gastroenterol 2001;96:689-96

Domperidone - Effective for FD in placebo-controlled trials

- Double-blind, placebo-controlled trials

Study Design	Number of Patients	Dose (mg/day)	Result	Reference
1 Double-blind, randomized	54	30	Positive effect but not superior to placebo	(83)
2 Double-blind, placebo-controlled	40	30	Superior to placebo	(84)
3 Double-blind, placebo-controlled, crossover	41	30	Superior to placebo	(85)
4 Double-blind, placebo-controlled	14	60	Superior to placebo	(48)
5 Double-blind, placebo-controlled	16	60	Superior to placebo	(25)
6 Double-blind, placebo-controlled, crossover	44	30	Superior to placebo	(86)
7 Double-blind, placebo-controlled	20	20	Positive effect	(87)
8 Double-blind, placebo-controlled	20	80	Superior to placebo	(97)
9 Double-blind, placebo-controlled	71	60	Superior to placebo	(98)

- **S/E**
 - Not crossing blood-brain barrier
 - Hyperprolactinemia (10-15%)



Reddymasu SC, et al. Am J Gastroenterol 2007;102:2036-45

Domperidone

- May be not effective for GERD

- 23 GERD patients
- Cross-over
 - Domperidone for 4 weeks
 - Placebo for 4 weeks
- Similar effect to placebo
- 45 GERD patients
- Ranitidine only vs Ranitidine + Domperidone
- RCT for 6 wks
- No significant difference in symptomatic relief

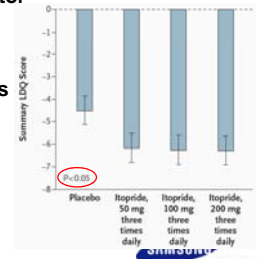
Maddern G.J. et al. J Clin Gastroenterol 1996; 8:135-40
 Masci E. et al. Drugs Exp Clin Res 1985;11:687-92



Itopride

- Effective for FD in early RCT

- Mechanism
 - Dopamine₂ receptor antagonist
 - Acetylcholin-esterase inhibitor
- Phase II RCT
 - 554 FD patients
 - Itopride vs Placebo for 8 wks
 - Response rate
 - 59.9% vs 41.2%
 - No extrapyramidal S/E



Holtmann G. et al. N Engl J Med 2006;354:832-40



Itopride

- Conflicting results for FD in phase III RCTs

- 1170 FD patients in 2 RCTs
- RCT: Itopride (100mg tid) vs Placebo
- 8 weeks
- Response rate

Parameter and time point	Category	International trial		p Value*	North American trial		p Value*
		Placebo (n = 248)	Itopride (n = 261)		Placebo (n = 291)	Itopride (n = 204)	
GPI* week 8 LDQ†	Symptom free, n (%)	34 (13.7)	42 (16.1)	0.62	21 (7.6)	27 (13.0)	0.45
	Markedly improved, n (%)	79 (31.8)	76 (29.1)		91 (31.3)	88 (28.9)	
	Slightly improved, n (%)	51 (20.8)	64 (24.5)		86 (27.2)	97 (31.8)	
	Unchanged, n (%)	98 (39.8)	82 (23.8)		105 (33.2)	77 (25.2)	
	Worse, n (%)	18 (7.3)	17 (6.5)		13 (4.3)	19 (4.9)	
	Responder, n (%)	117 (45.4)	118 (45.0)		115 (39.4)	115 (37.7)	
LDQ questions 1 and 8† week 8 LDQ†	Responder, n (%)	129 (52.4)	142 (54.8)	0.31	204 (69.8)	189 (62.2)	0.32
	Non-responder, n (%)	112 (44.5)	105 (40.2)		89 (30.2)	77 (26.2)	
LDQ Questions 1 and 8† week 8 LDQ†	Responder, n (%)	128 (52.7)	150 (57.0)	0.04	138 (44.8)	139 (46.8)	0.54
	Non-responder, n (%)	113 (47.3)	97 (38.0)		129 (45.2)	156 (53.3)	

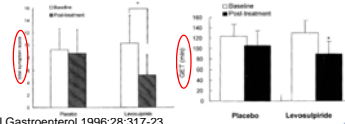
Talley NJ. et al. Gut 2008;57:740-6



Levosulpride

- Effective for FD in early RCT

- Mechanism
 - Dopamine₂ receptor antagonist
 - 5-HT₄ receptor agonist: partial → Ach release
- Italian RCT
 - 1298 FD patients
 - Levosulpride (25 mg tid) vs Placebo for 4 weeks
 - Sx score, GET: Significantly superior to placebo



Corrazza GR. et al. Ital J Gastroenterol 1996;28:317-23
 송치욱, 등. 대한내과학회지 1998;13:15-21



Levosulpride

- Side effect

- Drug-induced parkinsonism: 1-9.4%
- Levosulpride-induced movement disorder
 - 132 Korean patients
 - 85 parkinsonism, 9 tardive dyskinesia

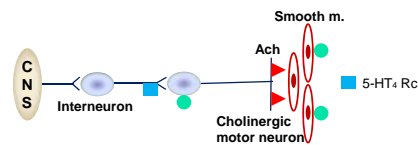
	Reversible LIM	Irreversible LIM	P value
Parkinsonism, n (%)	27 (51.9)	18 (100)	
Age (year), mean ± SD	68.9 ± 7.1	68.2 ± 8.2	0.79
Female, n (%)	22 (81.5)	15 (100)	0.08
Symmetric parkinsonism, n (%)	22 (81.5)	15 (100)	0.09
Rest tremor, n (%)	11 (40.7)	10 (100)	0.96
Duration of taking levosulpride (months), mean ± SD	18.1 ± 22.1	12.0 ± 11.0	0.29
Dosage of levosulpride (mg), mean ± SD	70.0 ± 15.8	83.4 ± 29.7	0.21
Tardive dyskinesia, n (%)	3 (33.3)	0 (0)	
Age (year), mean ± SD	64.3 ± 11.0	73.3 ± 7.1	0.17
Female, n (%)	3 (100)	3 (50)	0.13
Combined with parkinsonism, n (%)	2 (66.7)	4 (66.7)	<0.099
Duration of taking levosulpride (mg), mean ± SD	27.2 ± 21.6	21.5 ± 16	0.67
Treatment with benzodiazepines, n (%)	1 (66.7)	4 (66.7)	0.19
Isolated tremor, n (%)	3 (100)	0 (0)	N/A

Shin HW. et al. Movement Disorder 2009;24:2449-53



5-HT₄ Receptor Agonist

- Increasing release of Ach from cholinergic excitatory neurons
- Inducing peristaltic contraction



Cisapride/Tegaserod

- Withdrawal from market

- Cisapride**
 - 2000
 - Cardiac arrhythmia
 - Blocking K channel
 - Unrelated to 5-HT₁ agonism
 - Benzamide structure (C₆H₅CONH₂)
- Tegaserod**
 - 2007
 - Stroke
 - Cardiovascular ischemia

Mosapride

- Conflicting results for FD

- Benzaminide derivative, No effect on K channel
- European RCT
 - 606 FD patients
 - Mosapride vs Placebo for 6 weeks
- Korean study with single arm
 - 129 FD patients
 - Sx improvement after 4 wks compared to baseline Sx
 - No placebo comparison

Symptom improvement	Placebo n (%)	Mos 5 mg b.i.d. n (%)	Mos 10 mg b.i.d. n (%)	Mos 7.5 mg t.i.d.s n (%)	P value
Not improved	58 (14.0)	56 (4.0)	56 (3.9)	54 (3.8)	0.996
Improved	348 (86.0)	83 (5.9)	84 (5.9)	87 (6.1)	
Missing	1 (1)	1 (1)	1 (2)	1 (1)	

Hallerback BI, et al. Aliment Pharmacol Ther 2002;16:959-67
 조유경, 등. 대한소화기학회지 2004;43:1160-167

Mosapride

- May be effective adjuvant to PPI in GERD in Asia

- Indian RCT
 - 61 GERD patients
 - Group A: Pantoprazole only for 8 weeks
 - Group B: Pantoprazole + Mosapride for 8 weeks
- Japanese study with single arm
 - 44 PPI-resistant NERD patients
 - Omeprazole + Mosapride for 12 weeks
 - Sx improvement in patients with delayed gastric emptying versus patients with normal emptying

	Non-erosive GERD (29)		P	Erosive esophagitis (32)		P
	Group A (26)	Group B (3)		Group A (13)	Group B (19)	
Responded	17	2	0.6	6	18	0.001
Not responded	3	2		7	1	

Madan K, et al. Dis Esophagus 2004;17:274-8
 Futagami S, et al. J Gastroenterol 2010;45:413-21

Motilin

- Endogenous peptide that is cyclically released during the interdigestive state
- Stimulating gut motility through its action at gut receptors
 - Stomach > Small bowel > Terminal ileum
- Inhibiting gastric accommodation

Erythromycin

- May be effective for gastroparesis in small studies

- Macrolide antibiotics
- Mechanism
 - Direct action at motilin receptors on smooth muscle and on enteric nerves → GI smooth muscle contraction
 - Increased LES pressure by stimulation of cholinergic nerves

Erythromycin

- May be effective for gastroparesis in small studies

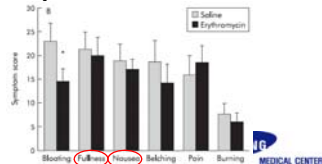
Author/year/reference	Study design	No. of subjects	Types of patients	Intervention	Length of study	Outcome results
Janssens et al., 1990 ¹⁰⁶	Open label	10	Diabetic gastroparesis	Erythromycin 250 mg TID	4 wk	Improved symptoms and gastric emptying
Dull et al., 1990 ¹⁰⁷	Open label	1	Scleroderma gastroparesis	Erythromycin 200 mg TID	9 mo	Improved symptoms and gastric emptying
Mozwez et al., 1990 ¹⁰⁸	Open label	1	Postvagotomy gastroparesis	Erythromycin 250 mg QID	2 wk	Improved symptoms
Kütman and Eisenach, 1992 ¹⁰⁹	Open label	2	Idiopathic gastroparesis	Erythromycin 200 mg QID	6 mo	Improved symptoms and gastric emptying
Erbas et al., 1993 ¹¹⁰	Single-blind, randomized, crossover	13	Diabetic gastroparesis	Erythromycin 250 mg TID	3 wk	Symptoms improved in 11 of 13 patients by 75%. Gastric emptying improved by 26%
Richards et al., 1993 ¹¹¹	Open label	10	Diabetic gastroparesis (2) Idiopathic gastroparesis (8)	Erythromycin 250 mg QID	4 wk	Symptoms improved in 7 of 10 patients by 20%. Gastric emptying improved by 43%
Ramirez et al., 1994 ¹¹²	Open label	9	Postsurgical (total vagotomy and antrectomy)	Erythromycin 150 mg TID	2 wk	Symptoms improved in 3 of 9 patients by 15%. Gastric emptying improved by 40%

Janssens J, et al. N Engl J Med 1990;322:1028-31
 Parkman HP, et al. Gastroenterology 2004;127:1592-1622

Erythromycin

- Not effective for FD in RCT

- 24 FD patients with delayed gastric emptying
- RCT: Erythromycin (200mg iv) vs Placebo
- Gastric emptying time acceleration
 - Erythromycin >> Placebo
 - Significant difference
- Meal-related symptom improvement
 - Overall: no difference
 - Only bloating



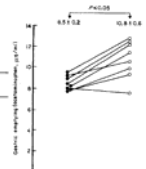
Arts J. et al. Gut 2005;54:455-60

Combination of Prokinetics

- Possible role in refractory cases

- FD: heterogeneous underlying pathophysiology
- Prokinetics with different mechanisms
- FD patients
- Cisapride only vs Cisapride + Domperidone
- RCT for 1 week
- GI symptom, Gastric emptying time

Gastrointestinal symptoms*	Cisapride + placebo	Cisapride + domperidone
Epigastric pain	1.0 ± 0.2	0.9 ± 0.2
Epigastric fullness	1.9 ± 0.3	0.5 ± 0.2†
Heartburn	0.9 ± 0.1	0.9 ± 0.1
Belching	1.0 ± 0.0	0.4 ± 0.2†
Nausea	1.1 ± 0.1	0.4 ± 0.2†



Tatsuta M. et al. Aliment Pharmacol Ther 1992;6:221-8

Summary

- Functional dyspepsia
 - Meta-analysis: Domperidone
 - Conflicting results: Itopride, Mosapride, Erythromycin
 - Effective, but S/E: Metoclopramide, Levosulpiride
- GERD
 - Insufficient data: Domperidone, Mosapride, Itopride
- Constipation
 - Promising results: Prucalopride

