

NIZATIDINE AMELIORATES GASTROPARESIS AND SLOW TRANSIT CONSTIPATION IN PARKINSON'S DISEASE

Hypothesis / aims of study

Gut disorder significantly affects quality of life of patients with Parkinson's disease (PD), since it leads to gastroparesis (bloating, nausea, vomiting), interfering with levodopa absorption (motor delayed-on, malignant syndrome), constipation, and in most advanced cases, intestinal pseudo-obstruction (ileus) and stercoral (stool) ulcer ¹. Previously drugs that act on myenteric dopamine / 5-hydroxytryptamine [5-HT, serotonin] receptors have been used to treat gut disorder in PD, showing variable benefits. The aim of this study is to present the results of our ¹³C-sodium acetate expiration breath and colonic transit time (CTT) analyses before and after administration of nizatidine (NZT) [figure1] that acts on histamine H₂-receptors in patients with PD.

Study design, materials and methods

Twenty patients with PD were enrolled in the study. They were 13 men and 7 women; age, 68.0 ± 7.72 years; disease duration, 5.50 ± 3.62 years. All patients underwent a gastrointestinal questionnaire, the breath test and the CTT test before and after 3months, 300 mg/day administration of NZT. Statistical analysis was performed by Student's *t*-test.

Results

NZT was well tolerated by all patients and none had abdominal pain or other adverse effects. 1) Tmax (¹³C) in PD patients did not change significantly after administration of nizatidine (NZT). Since Tmax (¹³C) in PD patients before NZT was diverse, according to the normative data, we divided them into two groups; e.g., delayed group (Tmax (¹³C) ≥ 60 min, Tmax (¹³C) 69.5±13.9 min [mean ± S.D.], n=11) and normal group (Tmax (¹³C) < 60 min, Tmax (¹³C) 42.2 ± 8.33 min [mean ± S.D.], n=9). As a result, NZT has shortened Tmax (¹³C) in delayed group (p<0.05) [figure2]. This acceleration was not noted in normal group (no statistical significance).

2) NZT shortened total CTT and rectosigmoid CTT particularly in the delayed group (total CTT ≥ 39 hours, n=12) (p<0.05) [figure3].

Interpretation of results

NZT is a selective histamine H₂-receptor antagonist, originally manufactured as a drug to treat peptic ulcer. However, in contrast to other H₂-receptor antagonists (cimetidine, famotidine, or ranitidine, famotidine) that lack prokinetic property, NZT has a clear prokinetic effect on the gut in experimental animals ² and in humans. ³ Therefore, while inhibiting gastric acid secretion via H₂-receptor antagonism, NZT promotes gut motility. NZT's prokinetic effect is thought to act on myenteric acetylcholine esterase. Ueki et al.² reported that the prokinetic effect of NZT is the result of increases acetylcholine activity by its noncompetitive inhibition of acetylcholine esterase. Increased acetylcholine in the myenteric plexus may directly stimulate gut motility. Acetylcholine is known to facilitate ghrelin (a potent gastric hormone) secretion. Therefore, increased acetylcholine might further facilitate gastric motility via hypothalamic stimulation by ghrelin.

Concluding message

Although this is a pilot study, we found a significant shortening of gastric emptying time and CTT after administration of NZT in PD patients. Since gut disorder directly relates with levodopa absorption, it might be possible that NZT further improves motor disorder (delayed-on) in PD. NZT can become a unique option to treat gut disorder in PD particularly in difficult cases.

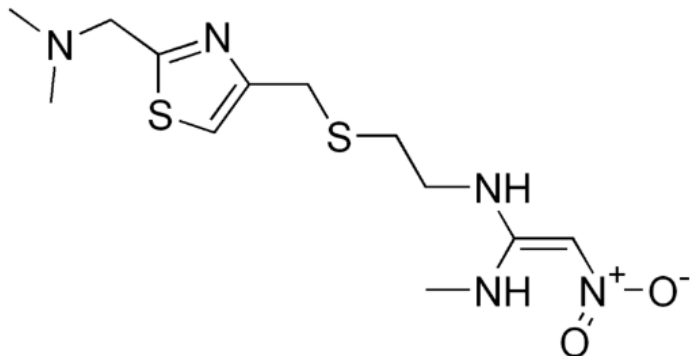


Figure 1 Chemical structure of nizatidine.

Nizatidine is a selective histamine H₂-receptor antagonist and a potent inhibitor of gastric acid secretion. It is considered to be equipotent with ranitidine but differs by the substitution of a thiazole-ring in place of the furan-ring in ranitidine.

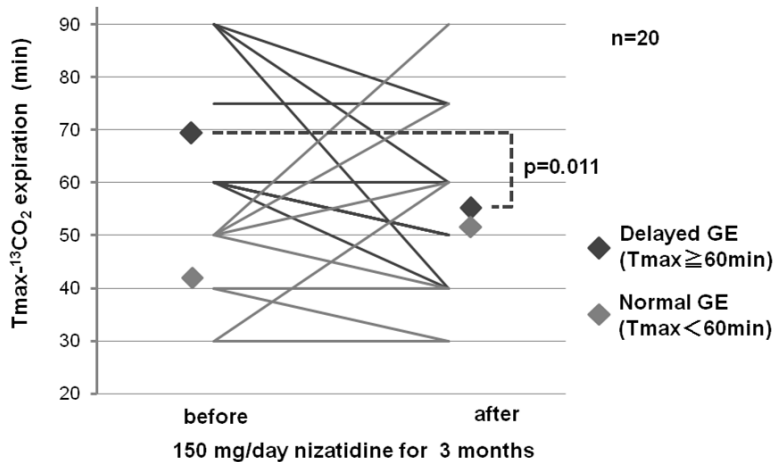


Figure 2 Effect of nizatidine on gastroparesis in Parkinson's disease patients.

Overall $T_{max} (^{13}C)$ in PD patients did not change significantly after administration of nizatidine (NIZ). Since $T_{max} (^{13}C)$ in PD patients before NIZ was diverse, according to the normative data, we divided them into two groups; e.g., delayed group ($T_{max} (^{13}C) \geq 60$ min, $T_{max} (^{13}C) 69.5 \pm 13.9$ min [mean \pm S.D.], $n=11$) and normal group ($T_{max} (^{13}C) < 60$ min, $T_{max} (^{13}C) 42.2 \pm 8.33$ min [mean \pm S.D.], $n=9$). As a result, NIZ has significantly shortened $T_{max} (^{13}C)$ in delayed group ($p < 0.05$). Several patients had the same data so that the line was overlapped.

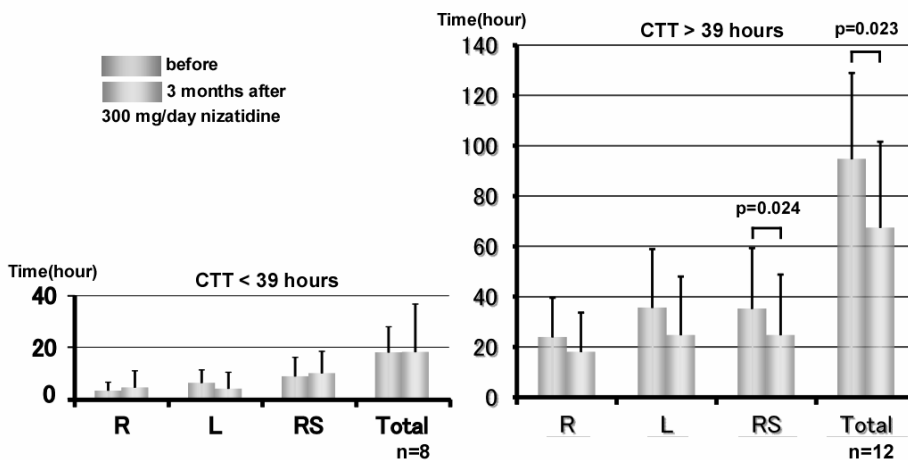


Figure 3 Effect of nizatidine on slow transit constipation in Parkinson's disease patients. Overall CTT in PD patients suggested a shortening (total CTT 47.7 hours) while none of them did not reach statistical significance. Since CTT in PD patients before NIZ was diverse, according to the normative data, we divided them into two groups; e.g., delayed group (total CTT ≥ 39 hours, $n=12$: total CTT 94.7 hours) and normal group (total CTT < 39 hours, $n=8$: total CTT 18.0 hours). As a result, NIZ has significantly shortened total CTT ($p=0.023$) and rectosigmoid CTT in delayed group ($p=0.024$) (total CTT 67.4 hours; right 18.0 hours, left 24.7 hours, rectosigmoid 24.7 hours). R: right L: left RS: rectosigmoid

References

1. Transdermal Dopamine Agonist Ameliorates Gastric Emptying in Parkinson's Disease. Tateno H, Sakakibara R, Shiina S, Doi H, Tateno F, Sato M, Masaka T, Kishi M, Tsuyusaki Y, Aiba Y, Ogata T, Suzuki Y. *J Am Geriatr Soc.* 2015 Nov;63(11):2416-8.
2. Ueki S, Seiki M, Yoneta T, Aita H, Chaki K, Hori Y, Morita H, Tagashira E, Itoh Z. Gastroprokinetic activity of nizatidine, a new H₂-receptor antagonist, and its possible mechanism of action in dogs and rats. *J Pharmacol Exp Ther* 1993; 264: 152–157.
3. Futagami S, Shimpuku M, Song JM, Kodaka Y, Yamawaki H, Nagoya H, Shindo T, Kawagoe T, Horie A, Gudis K, Iwakiri K, Sakamoto C. Nizatidine improves clinical symptoms and gastric emptying in patients with functional dyspepsia accompanied by impaired gastric emptying. *Digestion* 2012; 86: 114–121.

Disclosures

Funding: We have no sponsors. **Clinical Trial:** No **Subjects:** HUMAN **Ethics Committee:** Ethisc Committee in Sakura Medical Center, Toho University **Helsinki:** Yes **Informed Consent:** Yes