Effect of daikenchuto (TU-100) on gastrointestinal and colonic transit in humans


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Daikenchuto (TU-100) is a traditional Japanese medicine (Kampo medicine) that has been used to treat adhesive bowel obstruction (18, 20). TU-100 is a mixture of extract powders from dried Japanese pepper, processed ginger, ginseng radix, and maltose powder. Intraduodenal and intrajejunal administration of TU-100 (0.5, 1.5, and 3.0 g/dog) increased motility of the duodenum, proximal jejunum, and distal jejunum in conscious dogs in a dose-dependent manner (21). In in vivo experiments, the effect of TU-100 on laparotomy-induced or chemically induced intestinal dysmotility was inhibited by treatment with atropine or a 5-HT4 antagonist (30, 36). In vitro experiments, TU-100 stimulated contractions in isolated guinea pig ileum and increased spontaneous contractions of isolated rabbit jejunum (35), but it did not affect uterine motility (28). These effects were completely suppressed by treatment with atropine or tetrodotoxin, and partially suppressed by treatment with a 5-hydroxytryptamine receptor 4 (5-HT4) antagonist (41). TU-100 also stimulated acetylcholine release in ileal smooth muscle (34). These results suggest that the effects of TU-100 in the gastrointestinal (GI) tract are mediated mainly by cholinergic and serotonergic nerves.

No significant safety issues have been identified in preclinical studies of TU-100 in the dosing range intended for human use (1). Using the Functional Observational Battery (FOB) method, TU-100 at 1,800 mg/kg did not have any adverse effects on the general physical condition or behavior of the animals. Safety in humans is illustrated by the observations with widespread use of TU-100 in Japanese patients. Thus only 113 spontaneous adverse events associated with use of TU-100 have been reported from April 1, 1994 until June 30, 2008. Earlier trials of TU-100 suggested its prokinetic effects may be useful in treating GI hypomotility (17, 39). Previous studies of TU-100 in humans have involved postoperative patients after GI surgery, and they showed TU-100 prevented postoperative ileus (16, 20). The effects of TU-100 in humans without previous major GI surgeries are unclear.

The aim of this study was to evaluate the effects of orally administered TU-100 on GI and colonic transit and bowel function in healthy subjects.

MATERIALS AND METHODS

Participants. Sixty healthy subjects aged between 18 and 65 yr were recruited by advertisement and enrolled in the study. These subjects were either healthy men or nonpregnant, non-breast-feeding healthy women with body mass index (BMI) between 18 and 35 kg/m² and no alarm indicators suggesting disease or GI symptoms by
In this meal, technetium (99mTc)-sulfur colloid was used to label two scrambled eggs that were eaten with one slice of whole wheat bread and one glass of whole milk (300 kcal). This meal facilitated measurement of gastric and small bowel transit. Subjects ingested standardized meals for lunch and dinner at 4 h (550 kcal) and 8 h (750 kcal) after the radiolabeled meal. The subject left the study center at the end of the afternoon and returned the next 2 days (visits 4 and 5) for the images at 24 and 48 h. The images were obtained before breakfast after a minimum of 8 h of fasting on the second and third day of imaging. Relative to the time of breakfast meal ingestion, anterior and posterior gamma camera images were obtained every hour for the first 6 h (the first 4 h for the assessment of gastric emptying), and at 8, 24, and 48 h after ingestion of 111In capsule. The performance characteristics of this test in health and functional gastrointestinal disorders are summarized elsewhere (11, 13).

Transit data analysis. A variable region of interest program was used to quantify the counts in the stomach and each of four colonic regions: ascending (AC), transverse (TC), descending (DC), and combined sigmoid colon and rectum (RS). These counts were corrected for isotope decay, tissue attenuation, and downscatter of 111In counts in the 99mTc window (4, 5, 7, 8, 11).

Geometric mean of counts in anterior and posterior gastric regions of interest was used to estimate the proportionate gastric emptying over time of counts from 99mTc. The proportion of 99mTc reaching the colon at 6 h was estimated as a measure of orocecal (and a surrogate for small bowel) transit.

Geometric center (GC) of colonic counts at 4, 8 and 24 h was estimated using geometric mean of counts in AC, TC, DC, and RS, and stool (weighted by factors of 1 to 5, respectively). The primary variable of interest in overall colonic transit was the GC at 24 h.

The GC is the weighted average of counts in the different colonic regions: AC, TC, DC, RS, and stool. At any time, the portion of colonic counts in each colonic region is multiplied by its weighting factors as follows:

Fig. 1. Study design.
Effect of TU-100 on overall colonic transit. The mean colonic GE at 24 h of the placebo group was 2.29 (±0.24), compared with 2.51 (±0.17) and 2.55 (±0.20) of the TU-100 7.5 and 15 g/day group, respectively (P = 0.63). The mean

Table 3. Overall treatment effect of TU-100 on gastrointestinal transit and bowel functions

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Placebo n = 21</th>
<th>TU-100 (7.5 g/day), n = 19</th>
<th>TU-100 (15 g/day), n = 20</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GE t1/2, min</td>
<td>125.4 ± 6.0</td>
<td>134.6 ± 6.0</td>
<td>123.9 ± 6.1</td>
<td>0.45</td>
</tr>
<tr>
<td>GC 4</td>
<td>0.51 ± 0.16</td>
<td>0.71 ± 0.13</td>
<td>0.51 ± 0.11</td>
<td>0.54</td>
</tr>
<tr>
<td>GC 24</td>
<td>2.29 ± 0.24</td>
<td>2.51 ± 0.17</td>
<td>2.55 ± 0.20</td>
<td>0.63</td>
</tr>
<tr>
<td>GC 48</td>
<td>3.43 ± 0.25</td>
<td>3.75 ± 0.23</td>
<td>3.77 ± 0.25</td>
<td>0.64</td>
</tr>
<tr>
<td>Colonic filling at 6 h, %</td>
<td>40.3 ± 7.2</td>
<td>54.9 ± 6.3</td>
<td>34.0 ± 5.4</td>
<td>0.04</td>
</tr>
<tr>
<td>AC emptying t1/2, h</td>
<td>18.8 ± 2.3</td>
<td>13.1 ± 1.3</td>
<td>15.8 ± 1.5</td>
<td>0.07</td>
</tr>
<tr>
<td>Stool frequency, no. per day</td>
<td>1.13 ± 0.49</td>
<td>1.11 ± 0.46</td>
<td>1.21 ± 0.50</td>
<td>0.80</td>
</tr>
<tr>
<td>Stool consistency (BSFS 1-7)</td>
<td>3.63 ± 0.99</td>
<td>3.94 ± 0.79</td>
<td>3.61 ± 0.83</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Values are means ± SE. BSFS, Bristol Stool Form Scale. P value for overall treatment effects, analysis of covariance.
colonic GC at 48 h of the placebo group was 3.43 (±0.25), compared with 3.75 (±0.23) and 3.77 (±0.25) of the TU-100 7.5 and 15 g/day group, respectively (P = 0.64). Although there was a numerical difference in colonic transit on both doses of TU-100, these values were not significantly different from placebo treatment (Table 3).

Effect of TU-100 on bowel function. The mean stool number per day on placebo was 1.13 (±0.49), compared with 1.11 (±0.46) and 1.21 (±0.50) on TU-100 7.5 and 15 g/day, respectively. The mean stool consistency according to Bristol Stool Scale on placebo was 3.63 (±0.99), compared with 3.94 (±0.79) and 3.61 (±0.83) on TU-100 7.5 and 15 g/day, respectively. There were no significant overall treatment effects on stool frequency or consistency.

Adverse events. The proportion of participants developing headache was 42.8% of the placebo group, 36.8% of the 7.5 g/day of TU-100 group, and 40.0% of the 15 g/day of TU-100 group; no treatment differences were detected. In each group, the headache was mild and transient. Although very few adverse events were detected apart from headache, no treatment differences were detected for any of the adverse effects.

One participant who received 7.5 g/day of TU-100 in this study was noted to have an elevated serum creatine phosphokinase level and aspartate aminotransferase and alanine aminotransferase during follow-up approximately 1 mo after receiving the study medication. The patient presented to an emergency department complaining of muscle pain. The patient underwent extensive investigation including serological tests, electromyography, nerve conduction studies, and muscle biopsy. These showed antinuclear antibody 1:80 speckled pattern, normal nerve conduction studies, and mildly small motor unit potentials in a few extremity muscles with no fibrillation potentials or iterative discharges, and simple motor unit morphology compatible with a mild myopathy. However, skeletal muscle biopsy showed evidence of minimal inflammatory reaction with no evidence of myopathy, and detailed studies did not reveal any evidence for metabolic myopathy. At follow-up, 4 mo following ingestion of the study medication, all the biochemical abnormalities were normalized.

DISCUSSION

In this double-blind, randomized, placebo-controlled study, the herbal medication TU-100 accelerated colonic filling at 6 h and AC emptying $t_{1/2}$, suggesting a promotility effect on small bowel and ascending colon transit in healthy subjects. These data are consistent with previous animal studies (18, 19, 33, 34), which have shown that TU-100 increased dog intestinal motility in vivo (21). TU-100 evokes contractions in isolated intestine of rabbit and guinea pig (19, 33, 34).

One of the important results of the present study is that TU-100 (7.5 g/day) significantly accelerated AC emptying compared with placebo. Stivland et al. (37) showed that in patients with severe constipation the main transit disorder reflects delayed emptying of the proximal colon; in addition, the stimulation of transit in the proximal colon is retarded in irritable bowel syndrome (IBS) patients with constipation (IBS-C) (14). Therefore, significantly accelerated emptying of the proximal colon may lead to therapeutic benefit in patients with functional constipation or IBS-C in whom there is evidence of colonic transit delay (26). Significant acceleration of
AC emptying reduces the time for fluid absorption in this colonic region that has high absorptive capacity (12). Acceleration of AC emptying may therefore change stool consistency. The present study did not show statistically significant change in stool consistency in healthy subjects; however, the study was not powered to detect such a change in stool consistency. Further studies are needed in patients with constipation to assess the therapeutic potential of TU-100.

The observed acceleration of AC emptying may be in part due to the accelerated small bowel transit with delivery of a large volume of chyme to the ascending colon. It is conceivable that this results from its effects on serotonergic and cholinergic mechanisms that control motor functions. TU-100’s effects on small bowel and ascending colon transit may result from stimulation of small intestinal and colonic secretion of water and electrolytes, which may result from effects on serotonergic and cholinergic mechanisms. However, further studies are necessary to determine whether TU-100 promotes activation of chloride channels or induces chloride secretion through the cystic fibrosis transmembrane regulator (2). The present studies cannot differentiate between a primary effect on motility or secretion, with the latter inducing acceleration of transit. It is currently thought that acceleration of colonic transit with lubiprostone and linaclotide is secondary to secretory effects of those medications (38).

In the present study, there was no statistically significant difference between TU-100 at a dosage of 15 g/day and placebo. We considered the possibility of a type II error because of the relatively small sample size (n = 20 at doses of 7.5 and 15 g/day) treated with TU-100. However, the observed pooled coefficient of variation for AC emptying t1/2 was 48%, which was lower than the 53% used to estimate the required sample for the study. Further studies are needed to explore reasons for the lack of efficacy of AC emptying t1/2. Another possible explanation for the lack of a significant overall effect of TU-100 on overall colonic transit is that TU-100 has a dual effect on intestinal motility: a direct effect on smooth muscle and an effect on the neural pathways. In previous experimental studies, these effects resulted in either enhancement of normal function or normalization (reduction) of accelerated transit (35). These effects may have resulted in opposing effects on GI transit at the 15 g/day dose, whereby the dual effects resulted in balancing out of its actions, causing no significant difference in transit between TU-100 at a dosage of 15 g/day and placebo.

In previous studies in humans and animals that resulted in accelerated transit (22, 42), TU-100 was administered directly to the colon. It is conceivable that oral administration of TU-100 at doses of both 7.5 and 15 g/day did not result in sufficient concentrations reaching the colon to affect overall colonic transit. A medication delivery system that releases TU-100 at doses of both 7.5 and 15 g/day did not result in the expected acceleration of AC emptying (35). These effects may have resulted in opposing effects on GI transit at the 15 g/day dose, whereby the dual effects resulted in balancing out of its actions, causing no significant difference in transit between TU-100 at a dosage of 15 g/day and placebo.

In the present study, there was no statistically significant change in plasma motilin levels (29). On the other hand, it was shown that when TU-100 was administered via a long tube, there were no contractions stimulated in the parts of the GI tract proximal to where TU-100 directly contacted the GI mucosa (23). Moreover, TU-100-induced contractions were inhibited by intragastrointestinal pretreatment with lidocaine, suggesting a local pharmacological effect mediated at least in part by neural mechanisms (18), rather than depending on systemic absorption and redistribution to the digestive tract humorally.

We focused on bowel function and transit using noninvasive measurements because we have previously shown that these end points are responsive during short-term treatment with prokinetics such as velusetrag (TD-5108) (27). The magnitude of change in AC emptying and colonic filling at 6 h is in the range previously observed by the same methods with the prokinetics, tegaserod (32), prucalopride (3), renzapride (6), neurotrophin-3 (10), and velusetrag (27). Future studies with the same treatment duration and clinical end points, including pain and global IBS symptom relief, should address the clinical efficacy of TU-100 in IBS-C and chronic constipation.

In summary, our study demonstrated that TU-100 has a clinically significant prokinetic effect in small bowel and ascending colon transit in healthy subjects. TU-100 appears to be safe and well tolerated and is a potential treatment for IBS-C and functional constipation. Additional studies of TU-100 in randomized, controlled trials of subjects with IBS-C or functional constipation using both clinical and validated biomarkers such as small bowel and colonic transit measured by scintigraphy are warranted.

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DISCLOSURES

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REFERENCES


