Abatement of Morphine-Induced Slowing in Gastrointestinal Transit by Dai-kenchu-to, a Traditional Japanese Herbal Medicine

Tomonori Nakamura1,*, Akiko Sakai1, Issei Isogami1, Kazuhiro Noda1, Koichi Ueno2 and Shingo Yano1

Laboratories of 1Molecular Pharmacology and Pharmacotherapeutics and 2Geriatric Pharmacology and Therapeutics, Graduate School of Pharmaceutical Sciences, Chiba University, 1-33 Yayoicho, Inage-ku, Chiba 263-8522, Japan

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ABSTRACT—As a way of alleviating severe constipation in cancer patients taking morphine to relieve pain, effects of Dai-kenchu-to (DKT), a traditional Japanese herbal medicine (Kampo medicine), on gastrointestinal transit in mice or on the isolated guinea pig ileum were studied in special reference to morphine. Without altering the anti-nociceptive effect of morphine, DKT was significantly effective against morphine-induced disorder of gastrointestinal transit in mice as assessed by the charcoal meal test for the intestine and measurement of transit time for the colon tract. The results of in vitro studies with guinea pig ileum suggest that abatement of morphine-induced disorder of transit by DKT is caused by both moderate contraction of morphine-treated longitudinal muscle and relaxation of morphine-induced tonic contraction of circular muscle.

Keywords: Dai-kenchu-to, Morphine, Constipation

Morphine is the most effective antinociceptive agent known and is used to manage pain experienced by terminal cancer patients. However, it induces severe constipation, causing an obvious reduction in quality of life (QOL) (1). In a previous examination of records of cancer patients at a hospital (Chiba Rosai Hospital, Chiba), we found that 64.9% of patients who take morphine-containing drugs suffer from severe constipation (2). Other side effects were nausea and vomiting (43.9%), impairment of consciousness (less than 20%) and dysuria (less than 3%). Magnesium oxide or sennoside-containing drugs are typically administered for treatment of constipation, but it is difficult to control the dose of these drugs, and these therapies often become intolerable to the patients. Our survey also revealed that 5% of patients who take morphine-containing drugs stopped taking them due to severe constipation and that 54.0% of patients with constipation had to change their laxative because of ineffectiveness (2).

In the present paper, we demonstrate that the Japanese herbal medicine Dai-kenchu-to (DKT), which is frequently used to treat gastrointestinal disorders or post-operative ileum, lessens morphine-induced gastrointestinal disorders. There have been many studies of the effect of DKT on gastrointestinal disorders, but no pharmacological studies were performed with regard to morphine-induced constipation (3, 4); herein, we present pharmacological evidence that DKT is applicable for such a disorder.

All animal experiments were carried out according to the Principles of Laboratory Animal Care (NIH publication number 85-23, revised 1985) and Guidelines of the Animal Investigation Committee, Chiba University. Experiments were performed on male ddY mice (5 – 6-week-old; Takasugi Experimental Animals, Saitama) and male Hartley guinea pigs (300 – 450 g, Takasugi Experimental Animals). Animals were maintained on a 12 h light/dark cycle in a temperature-controlled animal colony and had ad libitum access to food and water prior to any procedure. Data were analyzed by the paired t-test and multiple-comparison (Dunnett’s test) tests. Differences at P<0.05 were considered statistically significant.

DKT (gift from Tsumura & Co. (Tokyo), Lot No. 2990100010) is a Kampo medicine that is composed of four crude drugs, dried ginger rhizome, ginseng root, rice gluten and Zanthoxylum fruit. In order to evaluate the effect of DKT on morphine-induced gastrointestinal (GI) transit, three other Kampo medicines were used as reference medicines: Sho-kenchu-to (SKT) (gift from Tsumura & Co., Lot No. 290099010), which has similar indications to DKT, and the ingredients of SKT are ginger rhizome, rice gluten, jujube fruit, cinnamon bark, glycyrrhiza root and peony root; Keishi-ka-shakuyaku-daio-to (KSDT)
induced inhibition was seen in a dose-dependent manner (Fig. 1A). The preventive effect of DKT against morphine-alone was also shown to significantly promote transit and KSDT, which contain rhubarb rhizome, were equi-

The effect of DKT on morphine-induced anti-nociception was studied by the formalin test and acetic acid-induced writhing test. In the writhing test, DKT did not significantly alter the anti-nociceptive effects of morphine (data not shown). Likewise, DKT did not change the anti-nociceptive effect of morphine in the first and second phases of the formalin test (Fig. 2).

To determine the effect of DKT on the basal or morphine-treated tone of the intestinal smooth muscle, measurement of contractile force was performed on guinea pig ileum by the Magnus method. Guinea pigs were euthanized with CO₂ and after laparotomy, the ileum was excised. Ileal segments (approximately 10–15 mm) were mounted longitudinally in an organ bath containing 32°C Krebs-Henseleit solution (112 mM NaCl, 5.9 mM KCl, 1.2 mM MgCl₂, 2.0 mM CaCl₂, 1.2 mM NaH₂PO₄, 25 mM NaHCO₃ and 11.5 mM glucose) gassed with O₂/CO₂ (19:1). Resting tension on the segments was adjusted to a load of 1.0 g, and then the segments were allowed to equilibrate for at least 60 min. Isotonic contraction was measured with an isotonic transducer connected to an amplifier. Ileal longitudinal muscle responded to DKT (10⁻³ g/ml) with moderate transient contractions (Fig. 3A) and the effects were observed in a dose-dependent manner from 10⁻³ to 10⁻ⁱ g/ml DKT (Fig. 3B). Contractions induced by 10⁻³ g/ml DKT were inhibited by addition of 1 μM morphine; however, application of 1 μM morphine alone did not influence longitudinal muscle contraction.

Circular muscle (approximately 5-mm width) was excised from the same area as longitudinal muscle. Isometric contraction of circular muscle was measured with an isometric transducer connected to an amplifier under 0.2-g tension in an organ bath filled with oxygenated (O₂/CO₂ (19/1)) 32°C-Krebs-Henseleit solution. After equilibration for at least 60 min, contraction tests were performed. DKT alone did not affect the basal tone of circular muscle, while 1 μM morphine alone raised the basal tone, indicating a lasting tonic contraction. The morphine-induced tonic contraction was completely attenuated by addition of 10⁻³ g/ml of DKT (Fig. 3C).

The present study has shown that DKT relieves morphine-induced delay of GI transit without affecting the...
antinociceptive effects of morphine. Furthermore, DKT causes moderate contraction of morphine-treated ileal longitudinal muscle and relaxation of morphine-induced contractions of ileal circular muscle. These effects of DKT on isolated intestine provide a pharmacological basis for recovery from morphine-induced disorder of GI transit. It has been recently demonstrated that GI transit may be coordinated by relaxation of the circular muscle and constriction of the longitudinal muscle through several neuronal networks including serotonin receptors (8, 9). This supports the previous work of Grider and Makhlouf who showed that morphine slows GI transit by inhibiting relaxation of the circular muscle and contraction of the longitudinal muscle (10).

DKT obviously showed improving effects against morphine-induced inhibition of intestinal and colonic transits, differently from three Kampo medicines of SKT, MNG and KSDT. The differential effects of DKT may be explained by crude drugs contained in DKT. Zanthoxylum fruit and ginseng root were contained in the three Kampo medicines SKT, MNG and KSDT. In the literature, however, there...
was no report that showed the acceleration of GI transit by ginseng root. In contrast, zanthoxylum fruit (Zanthoxylum piperitum) and its components such as hydroxy-β-sanshool and γ-sanshool have been shown to induce contraction of GI tract in guinea pig probably through mechanisms causing acetylcholine release from intrinsic cholinergic nerves and tachykinin release from sensory neurons. Accordingly, it is postulated that the accelerating effects of DKT on the rates of intestinal and colonic transits in morphine-treated mice would largely result from those of zanthoxylum fruit. The effect of hydroxy-β-sanshool was significantly inhibited by the capsaicin receptor antagonist, capsazepine (11). Another DKT component, (6)-shogaol, isolated from ginger, is reported to act on gastrointestinal motor neurons and facilitate an intestinal transit of charcoal after oral administration (12). Moreover, Onogi et al. have suggested that (6)-shogaol exhibits a capsaicin-like effect on the terminals of primary afferent nerves containing substance P, causing the initial release of neuropeptides and finally depleting the contents of neuropeptides, by subsequent stimulation of the primary afferents (13). Furthermore, Shibata et al. have reported that intragastric capsaicin stimulates colonic motility via a neural reflex (14).

Our results, together with findings from the above reports, indicate that the neuronal mechanism by which DKT relieves morphine-induced constipation is at least partly associated with stimulation of serotonin receptors (9) and vanilloid receptors (14) by components of DKT such as (6)-shogaol and hydroxy-β-sanshool. However, further studies are necessary to elucidate the relaxatory mechanism of DKT in morphine-induced tonic contraction.

REFERENCES

1. Mancini I and Bruera E: Constipation in advanced cancer patients. Support Care Cancer 6, 356 – 364 (1998)
2. Mizutani Y, Sakai A, Ueno K, Nakamura T, Takahashi H and Yano S: Report of an investigation of the use of morphine for cancer pain therapy and the digestive obstacles in the patients. J Jpn Soc Hospital Pharmacists 37, 233 – 236 (2001) (in Japanese)
3. Jin XL, Shibata C, Naito H, Ueno T, Funayama Y, Fukushima K, Matsuno S and Sasaki I: Intraduodenal and intrajejunal administration of the herbal medicine, dai-kenchu-tou, stimulates small intestinal motility via cholinergic receptors in conscious dogs. Dig Dis Sci 46, 1171 – 1176 (2001)
4. Tulimat MA, Ishiguchi T, Kurosawa S, Nakamura T and Taka-
hashi T: The inhibitory effect of herbal medicine – Dai Kenchu To (DKT) on the colonic motility in rats in vitro. Am J Chin Med 29, 111 – 118 (2001)

5 Niijima F, Tan-No K, Esashi A, Nakagawasai O, Tadano T, Takahashi N, Yonezawa A, Sakurada S and Kisara K: Inhibitory effect of intracerebroventricularly-administered [d-Arg², β-Ala⁴]-dermorphine(1 – 4) on gastrointestinal transit. Peptides 21, 295 – 299 (2000)

6 Ise Y, Katayama S, Hirano M, Aoki T, Narita M and Suzuki T: Effects of fluvoxamine on morphine-induced inhibition of gastrointestinal transit, antinoiception and hyperlocomotion in mice. Neurosci Lett 299, 29 – 32 (2001)

7 Broccardo M, Impota G and Tabacco A: Central tachykinin NK3 receptors in the inhibitory action on the rat colonic propulsion of a new tachykinin, PG-KII. Eur J Pharmacol 376, 67 – 71 (1999)

8 Shibata C, Sasaki I, Naito H, Ueno T and Matsuno S: The herbal medicine Dai-Kenchu Tou stimulates upper gut motility through cholinergic and 5-hydroxy-tryptamine 3 receptors in conscious dogs. Surgery 126, 918 – 924 (1999)

9 Prins NH, Akkermans LM, Lefebvre RA and Schuurkes JA: 5HT₄ receptors on cholinergic nerves involved in contractility of canine and human large intestine longitudinal muscle. Br J Pharmacol 131, 927 – 932 (2000)

10 Grider JR and Makhlouf GM: Role of opioid neurons in the regulation of intestinal peristalsis. Am J Physiol 253, 226 – 231 (1987)

11 Satoh K, Hashimoto K, Hayakawa T, Ishige A, Kaneko M, Ogihara S, Kurosawa S, Yakabi K and Nakamura T: Mechanism of atropine-resistant contraction induced by Dai-kenchu-to in guinea pig ileum. Jpn J Pharmacol 86, 32 – 37 (2001)

12 Yamaha J, Huang QR, Li YH, Xu L and Fujimura H: Gastrointestinal motility enhancing effect of ginger and its active constituents. Chem Pharm Bull (Tokyo) 38, 430 – 431 (1990)

13 Onogi T, Minami M, Kuraishi Y and Satoh M: Capsaicin-like effect of (6)-shogaol on substance P-containing primary afferents of rats: a possible mechanism of its analgesic action. Neuropharmacology 31, 1165 – 1169 (1992)

14 Shibata C, Sasaki I, Naito H, Tsuchiya T, Takahashi M, Ohtani N and Matsuno S: Intragastric capsaicin stimulates colonic motility via a neural reflex in conscious dogs. Gastroenterology 109, 1197 – 1205 (1995)