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이정수, 손창규, 조정효, 신장우, 유화승, 이연월, 이남헌, 윤담희, 조종관*

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The Effects of Agastache Rugosa Extract on Intestinal Motility

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Objectives : 본 연구는 암환자의 위장관 기능장애를 개선시킬수 있는 보다 효과적인 약물개발의 일환으로 곽향 추출물의 장운동에 미치는 영향을 평가하기 위해 수행되어졌다.

Methods : 생리적인 상태에서 곽향추출물이 장운동에 미치는 영향을 알아보기 위해 장운동촉진제인 carbachol과 곽향 추출물을 실험쥐들에게 투여후 15분후 charcoal meal을 먹여서 charcoal meal의 소장내 통과 정도를 비교 측정하였다. 또, loperamide, scopolamine, nicotine으로 장운동을 억제시켜 놓은 실험쥐들에게 15분 간격으로 곽향 추출물과 charcoal meal을 먹인 후 역시 charcoal meal의 소장내 통과 정도를 비교 측정하였다.

Results : 곽향 추출물은 생리상태에서는 장운동에 영향을 미치지 않았다. 곽향추출물은 loperamide와 scopolamine으로 유발된 장운동 억제상태에 대하여 부분적으로 영향을 끼쳤다. 그러나 nicotine으로 유발된 상태에 대해서는 영향을 끼치지 않았다.

Conclusion : 곽향 추출물은 소화관 기능부전 완화에 효과적으로 작용하는 천연물이라 추론할 수 있다.

Key Words: *Agastache Rugosa*, Gastrointestinal Dysfunction, Intestinal Motility

Ⅰ. Introduction

Conventional cancer treatment results in various disturbances of gastrointestinal function. Side-effects are regarded as a significant cause of mortality and morbidity in cancer patients and are also one of major complications in the course of natural cancer progression. Among these disturbances, intestinal stasis or ileus is related to intestinal motility and has been attributed by various causes, including concurrent physical, psycho-social and existential problems[1-5].

Many studies have been done on gastrointestinal disorders in cancer patients and they have been significant situations in the clinical setting. However, it is also not too surprising that there is no universally effective therapy for intestinal immobility as of current. Because a unifying mechanism has of yet been made to explain the symptomatic production in cancer patients with intestinal stasis or ileus[6].

In Korea, *Agastache rugosa* is a widespread herbal medicine mainly used for treatment of gastrointestinal diseases, including nausea, bloating, abdominal distension and pain. Especially in Dunsan Oriental

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Hospital of Daejeon University, *Agastache rugosa*, one of components of Baegieum, is an effective herbal formula for intestinal stagnation, has significant clinical effects on cancer patients with gastrointestinal disorders.

Agastache rugosa is known to have many pharmacological effects, such as anti-mycotic, anti-fungal, and anti-atherogenic effects[7-9]. However, as of yet, there has not been any studies done to perceive the effects on intestinal motility at physiological and pathological state. In our previous pilot study, we found that Baegieum improved the pathogenically suppressed intestinal peristalsis. Therefore, it may be persuaded that *Agastache rugosa* has some effects on intestinal motility, too.

In this study, we observed how *Agastache rugosa* extract (ARE) affects the passage of charcoal in laboratory mice.

II. Materials and Methods

1. Preparation of ARE

Agastache rugosa was obtained from Dunsan Oriental Hospital of Daejeon University. Fifty grams of *Agastache rugosa* were mixed with 1 L of distilled water and left for 1 h at room temperature, and then the whole mixture was boiled for 2 h. The extract solution was centrifuged for 30 min at 2,000 ×g and the supernatant was concentrated with vacuum evaporator (BÜCHI, Switzerland) and then lyophilized. The yield of ARE was 8.5% (w/w).

2. Chemical preparation

Carbachol, loperamide, scopolamine, and nicotine were purchased from Sigma (USA). Loperamide was dissolved with normal saline (0.1 mg/ml) containing 0.05% tween 80. The remaining drugs were dissolved with normal saline (0.9%). Charcoal (Wako, Japan) meal was made by suspension of 5% charcoal in 10% gum arabic solution.

3. Animals and treatment

Seven-week old male ICR mice were purchased from Samtako (Osan, Korea) and were housed in an environmentally controlled room at 22±2℃, relative humidity at 55±10% and 12 h light/dark, and fed with commercial pellets (Samtako, Korea) and tap water *ad libitum*. The mice were divided into 16 groups of 7 animals. After a five-day acclimation, the mice fasted for 24 hours. They were pre-treated respectively with loperamide(0.5 mg/kg, sc), scopolamine(0.25 mg/kg, sc), nicotine(1.5uM/kg, sc), and carbachol(0.5mg/kg, po). Afterwards they were administered with ARE after 15 min and charcoal meal after 30 min. Control groups were treated by the same manner with distilled water as a carrier of ARE. The travel rates of charcoal were recorded by calculating the percentage of passage distance of the entire small intestine after sacrifice by cervical dislocation at 20 minute after charcoal meal administration.

4. Statistical analysis

The results were expressed as mean ± SD. Statistical analysis of the data was carried out by the Student's t-test. A difference from the respective control data at the levels of $p<0.05$, $p<0.01$ was regarded statistically significant.

III. RESULTS

1. The physiological effects of ARE on intestinal motility

Mice were administered with ARE (25 mg/kg, 100 mg/kg) or carbachol (0.5mg/kg) before 15 min of charcoal meal to investigate if ARE has any

physiological effects on intestinal motility. There were no significant differences among these groups. Carbachol increased intestinal motility by 97%(Fig. 1.).

2. The effects of ARE on induced intestinal stagnation

Mice were pre-treated with loperamide (0.5 mg/kg, sc), scopolamine (0.25mg/kg, sc), and nicotine (1.5uM/kg, sc) to suppress intestinal motility. The mice were administered with distilled water or ARE (25mg/kg, 100mg/kg) to investigate if ARE affects the intestinal motility in suppressed condition. Loperamide treatment decreased intestinal motility by 22%. ARE treatment improved intestinal motility by 27% in a dose dependent manner($p<0.05$). ARE treatment also increased intestinal motility suppressed by scopolamine. However, ARE didn't affect intestinal activity suppressed by nicotine(Fig. 2, 3, 4.).

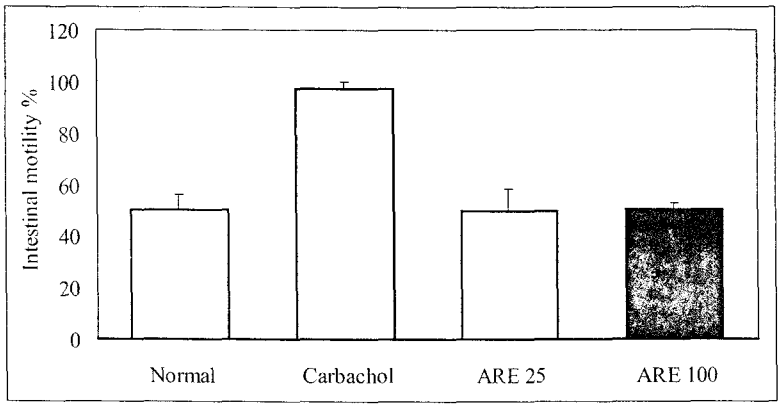

Fig. 1. The Physiological Effects of ARE on Intestinal Motility.

Mice were administered with ARE (25 mg/kg, 100 mg/kg) or carbachol (0.5 mg/kg) before 15 min of charcoal meal. Intestinal motility was determined at 20 min after administration of charcoal meal. The data were expressed as mean ± SD.

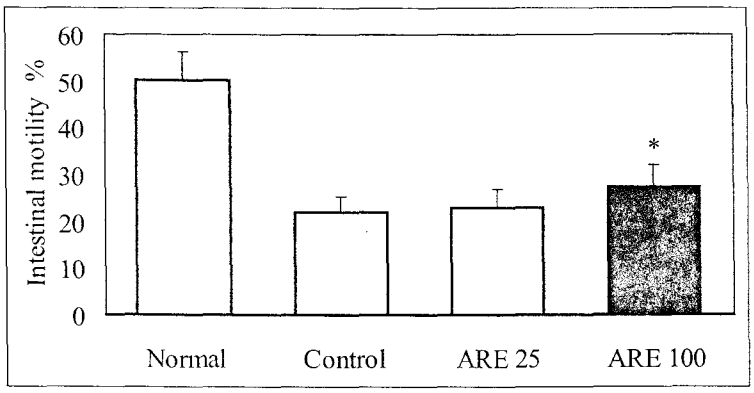

Fig. 2. The Effects of ARE on Induced Intestinal Stagnation by Loperamide.

Mice were administered with loperamide (0.5 mg/kg) and ARE (25 mg/kg, 100 mg/kg) before 30 min and 15 min of charcoal meal administration respectively. Intestinal motility was determined at 20 min after administration of charcoal meal. The data were expressed as mean ± SD (*P < 0.05).

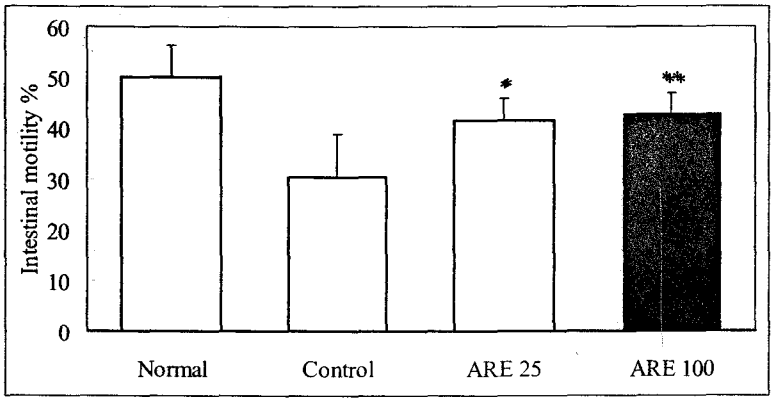

Fig. 3. Effect of ARE on intestinal motility at suppressed state by scopolamine.

Mice were administrated with scopolamine (0.25mg/kg, sc) and ARE (25mg/kg, 100mg/kg) before 30 min and 15 min of charcoal meal administration respectively. Intestinal motility was determined at 20 min after administration of charcoal meal. The data were expressed as the mean ± SD. Significant differences compared with control group (*P < 0.05, **P < 0.01).

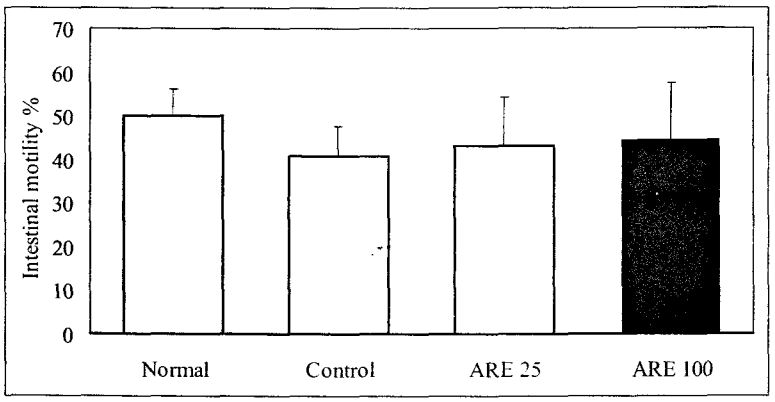

Fig. 4. Effect of ARE on intestinal motility at suppressed state by nicotine

Mice were administrated with nicotine (1.5 uM/kg, sc) and ARE (25 mg kg, 100 mg kg, po) before 30 min and 15 min of charcoal meal administration respectively. Intestinal motility was determined at 20 min after administration of charcoal meal. The data were expressed as the mean ± SD.

IV. Discussion

The etiology of ileus in cancer is multifactoral including autonomic neural dysfunction, inflammatory mediators, narcotics, gastrointestinal hormone disruptions and anaesthetics. These complications are due to abdominal surgery, chemotherapy, radiation, morphine, and other opioids[1-3].

Postoperative ileus occurs because of initially absent and subsequently abnormal motor function of the stomach, small bowel and colon. Several chemotherapy drugs caused peripheral neuropathy including adynamic ileus. In addition, gastrointestinal effects of morphine and other opioids may result in opioid-induced bowel dysfunction. These complications caused an obvious reduction in quality of life(QOL). Therefore, it is necessary to develop

effective medicinal agents for gastrointestinal dysfunction in cancer patients[1-5].

Although it has been well known that ARE is one of clinically important herbal medicine for cancer patients with intestinal stasis or ileus, we have insufficient knowledge about the role of ARE on the function of the digestive system. To achieve this basic answer, we measured the passage rate of charcoal after ARE treatment. This decision was based on the fact that intestinal motility directly or indirectly represents the state of health of alimentary canal. Here, we simply adapted four different mouse models, normal and loperamide, scopolamine and nicotine to induce a pathologic state[10-3].

Carbachol, a parasympathomimetic medicine which mimics the action of acetylcholine, increased intestinal motility in normal conditions by 97%. In contrast to carbachol, ARE didn't affect the passage rate of charcoal meal compared with control in normal condition[10]. Both groups(25mg/kg, 100mg/kg) presented same rate around 50% at twenty minutes after charcoal administration as shown in Fig. 2. This result could come from the general characteristics that herbal medicines don't show any pathology in healthy mice.

We also applied ARE to drug-induced pathological models which intestinal motility were suppressed by loperamide, scopolamine and nicotine. Loperamide, a peripheral μ-opioid receptor agonist, has been widely used as an antidiarrheal agent on gastrointestinal transit. Scopolamine, an alkaloid drug obtained from plants, are structurally similar to the nerve substance acetylcholine. It acts to interfere with the transmission of nerve impulses by acetylcholine in the parasympathetic nervous system and produces typical parasympathetic system depression symptoms. Nicotine, which is a ganglionic blocker, effects the prostaglandin-dependent gastric wave and antral motility[11-3].

In this experiment, loperamide treatment(0.5 mg/kg, sc) significantly decreased the travel rate of charcoal by around 22% comparing to 50% in the normal group. In comparison with loperamide, ARE stimuli slightly ameliorated the suppressed intestinal motility by 27% in the 100mg/kg concentration as shown in Fig. 2. But ARE didn't show any differences compared with loperamide treatment in 25 mg/kg concentration. ARE treatment also increased intestinal motility suppressed by scopolamine. Scopolamine treatment significantly decreased the travel rate of charcoal by around 30% comparing to 50% in the normal group. ARE stimuli significantly improved the suppressed intestinal motility by greater than 40% in both groups(25mg/kg, 100mg/kg) as shown in Fig. 3. However ARE didn't affect intestinal activity suppressed by nicotine as shown in Fig. 4.

These results meant that ARE might function to improve the pathogenically suppressed intestinal peristalsis. Also, it might be suggested that the effects of ARE is based on the action of acetylcholine release because it presented the most effective results in scopolamine group. However, it is not easy to conclude the mechanism of ARE based on this experiment and has to be studied further through advanced experimental models.

Based on these results, we can conclude that ARE can improve intestinal stasis or ileus by especially improving suppressed intestinal motility. Accordingly, our study might help explain the mechanisms which ARE can be applied scientifically for many similar disorders with this model in the clinical setting.

V. Conclusion

This experimental study was carried out to evaluate the effects of ARE on intestinal motility. The results were obtained as follows:

1. ARE didn't affect the intestinal motility at the physiological state.
2. ARE partially activated the intestinal motility at loperamide-induced suppressed state.
3. ARE significantly activated the intestinal motility at scopolamine-induced suppressed state.
4. ARE didn't affect the intestinal motility at nicotine-induced suppressed state.

From these results, it may be concluded that ARE can be an effective herbal drug for gastrointestinal dysfunction, especially when applied to cancer treatment.

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