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Laxative Effect of Ispaghula: Physical or Chemical Effect?

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Seed husk of *Plantago ovata* (ispaghula) is a popular laxative used to regulate bowel movements. It is generally believed that its laxative effect is mediated through its fibre and/or hydrophilic mucilloid contents. We demonstrate in this communication that it also contains active chemicals causing a laxative effect. An aqueous–methanol extract of ispaghula at a dose range of 1–10 mg/mL caused a dose-dependent stimulatory effect in guinea-pig ileum. Pretreatment of tissue with atropine (1 μM) completely blocked the contractile effect of a supra-maximal dose of acetylcholine (10 μM) similar to that of the lower doses of ispaghula (1–4 mg/mL), however, the effect of the larger doses (6 and 10 mg/mL) was blocked partially. These results indicate that the stimulatory effect of ispaghula at lower doses is mediated through an ACh-like mechanism and the effect of high doses was mediated partially through unknown mechanism(s). © **1998 John Wiley & Sons, Ltd.**

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INTRODUCTION

Plantago ovata or *P. espaghula* (Plantaginaceae) is indigenous to the Indo-Pak subcontinent and its seed husk (ispaghula) is a popular laxative, being extensively used in folk medicine (Nadkarni, 1976; Usmanghani *et al.*, 1997). In recent years, it has gained popularity all over the world and equally accepted by 'modern' physicians. In fact, it is one of the most commonly used over-the-counter preparations and millions of people worldwide now use ispaghula to regulate bowel habits.

Ispaghula has been extensively studied and found to be useful in chronic constipation (Borgia *et al.*, 1983), irritable bowel syndrome (Prior and Whorwell, 1987; Kumar *et al.*, 1987), ulcerative colitis (Hallert *et al.*, 1991) and diverticular disease (Eastwood *et al.*, 1978; Thorburn *et al.*, 1992). It is generally believed that its laxative effect is mediated through its fibre and/or mucilage contents (Brunton, 1996). However, its action is relatively prompt compared with other bulk-forming laxatives. It is possible that it contains active chemical(s) causing a laxative effect complementary to the physical effect. Interestingly, the presence of a cervical dilator substance, isaptent, has been reported in this plant (Khanna *et al.*, 1980). Similarly, some other systemic effects, such as antilipaemic (Anderson *et al.*, 1988; Turley and Dietschy, 1995) and hypoglycaemic (Mahapatra *et al.*, 1988) have also been reported, which suggests the presence of active chemicals in this plant. The aim of this study was to see whether it contains some active chemical(s) causing a laxative effect complementary to the bulk-forming effect.

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MATERIALS AND METHODS

Extraction of plant material. Ispaghula husk was purchased from a local market, extracted with 70% methanol (1:5) for 3 days at room temperature and filtered. The residue was extracted two more times. All the filtrates were combined and concentrated on a rotary evaporator under reduced pressure below 40°C. The yield of brown thick extract was approximately 2%. The extract was stored at −20°C until used for pharmacological studies and dissolved in distilled water on the day of the experiment.

Pharmacodynamic studies. Isolated guinea-pig ileum was used by the method previously used in our laboratory (Gilani *et al.*, 1997). Guinea-pigs of either sex (400–600 g) were killed by cervical dislocation and segments of ileum about 2 cm long were suspended in a 10 mL tissue bath filled with Tyrode's solution maintained at 37°C and aerated with 5% CO_2 in O_2. The composition of the Tyrode's solution was (mM): NaCl, 136.9; KCl, 2.7; $MgSO_4$, 1.1; KH_2PO_4, 0.4; D-glucose, 5.6; $NaHCO_3$, 11.9 and $CaCl_2$, 1.8 (pH 7.4).

An initial loading of 0.7 g was applied to the tissue and isotonic contractions to acetylcholine (ACh) were recorded through a Bioscience transducer (T_3) coupled with a Bioscience (PR 200) chart recorder. Following an equilibrium period of 30 min, the tissue was exposed for up to 20 s to a constant concentration of acetylcholine (0.5 μM) which produced a submaximal response, then

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the tissue was washed and the cycle repeated at 3 min intervals until constant responses were recorded (usually 10–15 contractions). Plant extract was tested similarly using bolus administration of various doses. In the preliminary experiments, ACh at a dose of 1–10 μM produced maximum contractions. In the subsequent experiments with ispaghula, the contractions induced by 10 μM of ACh was considered a maximum response and the contractile responses of ispaghula were compared with this response to ACh.

RESULTS AND DISCUSSION

The aqueous–methanol extract of ispaghula caused a dose-dependent contractile effect in guinea-pig ileum. The contractile effect was qualitatively similar to that of acetylcholine and its efficacy was compared with the maximal effect produced by acetylcholine (ACh), mediated at 10 μM (Fig. 1). The threshold response (2.1% ± 0.7%; mean ± SEM; $n = 8$) was obtained at 1 mg/mL, while the magnitude of contractions produced at 2 mg/mL was 21.5% ± 4.4% of the ACh maximum response. The next higher dose (4 mg/mL) caused a 56.6% ± 3.3% response and a dose of 6 mg/mL proved to be the maximal dose with an 85.1% ± 2.1% response of the control maximum. The highest dose of ispaghula used in this study was 10 mg/mL, which produced 81.3% ± 6.1% response which is similar to that obtained at 6 mg/mL.

To see whether the stimulatory effect of ispaghula is mediated through an ACh-like mechanism, the tissue was pretreated with atropine, a competitive blocker of acetylcholine at muscarinic receptors (Arunlakhshana and Schild, 1959; Gilani and Cobbin, 1986). When repeated in the presence of atropine (1 μM), the effect of a supramaximal dose of ACh (10 μM) was completely abolished, indicating a complete blockade of muscarinic receptors. Interestingly, the contractile effect of lower doses (1–4 mg/mL) of ispaghula was completely blocked similar to that of ACh, however, the responses of higher doses (6 and 10 mg/mL) were blocked partially with resulting contractions of 24.0% ± 4.7% and 5.1% ± 2.0% respectively (Fig. 1). This suggests that the stimulatory effect of ispaghula at lower doses, is mediated through stimulation of muscarinic receptors and the effect of higher doses was mediated partially through other mechanism(s) indicative of the presence of at least two components.

Histamine is also known to cause a stimulatory effect in the gut and to see whether the atropine-insensitive stimulatory effect of ispaghula is mediated through a histamine-like action, tissue was treated with mepyramine (1 μM), an H_1-receptor blocker (Rang and Dale, 1991). However, blockade of histaminergic receptors did not modify the response of higher doses (6–10 mg/mL) of ispaghula (data not shown) which rules out the possibility of histaminergic involvement.

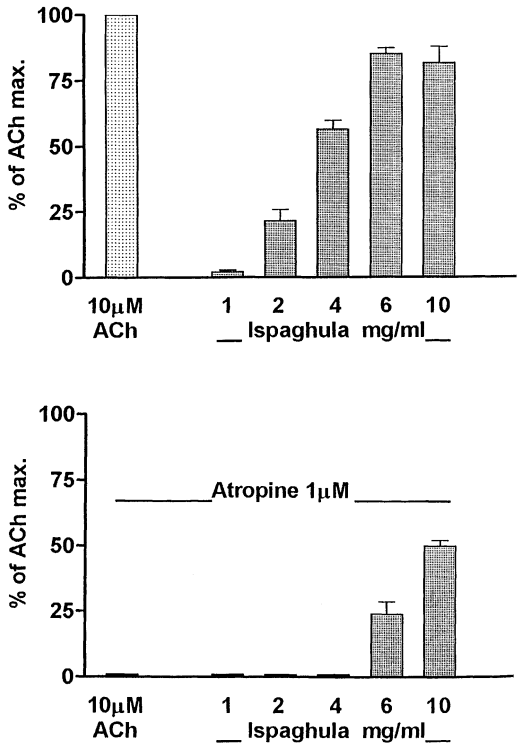

Figure 1. Comparison of acetylcholine and ispaghula for their contractile effect in the absence (upper panel) and presence of atropine (lower panel) in isolated guinea-pig ileum. Atropine was administered 20 min before the re-determination of agonist responses. The bar shows mean ± SEM of 8 determinations.

Multiple endogenous substances such as prostaglandins, VIP and nitric oxide (NO) are well known to cause a contractile effect in the gut and it is possible that the stimulatory effect of a high dose of ispaghula is mediated through such mechanism(s). Interestingly, isaptent (a preparation from ispaghula) has been reported to cause dilatation of the cervix (Khanna *et al.*, 1980) and have an abortifacient effect in pregnant women (Sakunthala *et al.*, 1983), the typical characteristics of prostaglandins (Graves, 1996). The precise mechanism of the second component of ispaghula would be rather speculative at this stage, however, the possibility of involvement of a prostaglandin-like mechanism cannot be ignored.

Thus the laxative effect of ispaghula may be due to its chemical contents in addition to the physical effect (bulk-forming fibre contents). Ispaghula is considered superior to other laxative drugs (Odes and Madar, 1991) and the presence of a combination of different chemical laxative constituents (reported in this study) along with the known physical effect, may be responsible for the better efficacy of ispaghula.

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