Research Article

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Antispasmodic Activity of SJ KIDDROPS, An Herbal Formulation Against Spasm of Smooth Muscle Preparation

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The antispasmodic effect of SJ KIDDROPS was studied in vitro on guinea pig Ileum and rat fundus against spasmogens: acetylcholine (Ach), histamine, 5-HT and barium chloride. SJ KIDDROPS (0.32 mg/ml of bath volume) shifted the concentration response curve of acetyl choline, histamine and barium chloride to right. Reduction of contraction with SJ KIDDROPS on ileum contractions induced by Ach, histamine and barium chloride were respectively 60.11%, 62.3% and 65.92%. Furthermore, the SJ KIDDROPS at a bath conc of (0.32 mg/ml of bath volume) shifted the concentration response curve of acetyl choline, and 5-HT to right with 75.6% and 66.75% reduction in the maximal response respectively. The blockade produced by SJ KIDDROPS on all spasmogen induced spasm on different smooth muscle is reversible. Oral administration of SJ KIDDROPS dose dependently reduced the intestinal transit in mice. Our results suggest that SJ KIDDROPS may be useful against smooth muscle spasm. These actions were probably mediated by distinct mechanisms.

Keywords: Antispasmodic, invitro, smooth muscle

INTRODUCTION

Spasm is a sudden violent involuntary muscular contraction or a transitory constriction of passage[1]. To relieve these types of spasm, antispasmodics are used. Antispasmodics are the drugs that relax the smooth muscle of the gut, used to treat indigestion not associated with peptic ulcers, irritable bowel syndrome, and of diverticular disease. Broadly, the anti-cholinergics/anti-spasmodics are used to relieve cramps or spasms of the stomach, intestine, and bladder. There is a limitation of antimuscarinic antispasmodics in children due to unusual excitement, nervousness, restlessness, or irritability, unusual warmth, dryness, and flushing of the skin which are more likely to occur and who are usually more sensitive to the effects of anti-cholinergics. When anti-cholinergics are given to children during hot weather, a rapid increase in body temperature may occur among infants and children-especially those with spastic paralysis or brain damage[2, 3]. Shortness of breath or difficulty in breathing has been observed in children administered with dicyclomine. Looking into the older perspectives and limitations of conventional anti-cholinergic, anti-spasmodics, there are needs to develop newer and safer anti-spasmodics for the management of broader types of spasmodic pain disorders in children. Anti-spasmodics are recommended to treat acute spasmodic or colicky pain.

The Indian system of medicine, Ayurveda cited several plants which are useful against various gastrointestinal disorders without any side effects. SJ KIDDROPS, an herbal formulation contains *Zingerber officinale* Roscoe, Zingiberaceae(rhizome), *Apium graveolens* L., Apiaceae (fruit) and *Foeniculum vulgare* Mill., Apiaceae (fruit). All these plants are proved to treat various gastrointestinal disorders[4, 5, 6]. For these reasons, we decided to assess the effect of SJ KIDDROPS formulation for spasmolytic activity in gastrointestinal spasm.

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MATERIALS AND METHODS

SJ KIDDROPS containing *Apium graveolens, Foeniculum vulgare* and *Zingiber officinale* was formulated by The Himalaya Drug Company, Bangalore.

Chemicals used

Acetyl choline chloride, 5-hydroxytryptamine creatinine sulphate, histamine diphosphate, Barium chloride. All other reagents used were of analytical grade. All drugs and SJ KIDDROPS were freshly prepared to desired concentrations with distilled water just before use.

Animals

Swiss albino mice, wistar rats, guinea pigs were used for the study. They are fed with standard pellet diet and water *ad libitum.*

Effect of SJ KIDDROPS on acetylcholine, histamine and barium chloride induced contractions of guinea pig ileum[7].

The method is followed as described by Kulkarni SK etal. Guinea pig of either sex weighing 250-300 gm were selected and kept without food overnight giving water *ad libitum.* The animals were sacrificed by stunning and carotid bleeding. Then they were cut opened and the ileum identified. A terminal portion of 2 cm after the 10 cm nearest to the ileo-caecal junction were isolated and placed in a shallow dish containing tyrode solution. Its lumen was gently cleaned out. Then the lumen was mounted in a 25 ml organ bath containing tyrode solution maintained at 37^0 C and bubbled with carbogen. The preparation was allowed to equilibrate for 45 min under 500mg tension. Contraction of the preparation was registered by an isotonic fine movement transducer, which is amplified and recorded by a single channel student physiograph. Dose response curves obtained with spasmogens like Ach, histamine and barium chloride were recorded. The SJ KIDDROPS (0.32mg/ml) was added to reservoir and allowed to act for 20 min. during which the preparation was washed every 5 min. with physiological salt solution. Dose response curves obtained with various spasmogens were compared with responses to the same concentration of spasmogens after the tissue has been bathed with 0.32mg/ml (bath volume) of test solution. The contact time of the agonist was 30 sec in a time cycle of 4 minutes. The percentage inhibition of the acetylcholine, histamine and barium chloride evoked contractions by SJ KIDDROPS was calculated by considering the maximum contraction obtained as 100%. The results expressed as arithmetic mean ± SEM. Minimum of 6 experiments were carried in each group.

Effect of SJ KIDDROPS on 5-HT and acetylcholine induced contractions of rat fundus[8]

Rats weighing 150-250 g of either sex were selected and kept without food overnight, giving water *ad libitum*. The animals were sacrificed by stunning and carotid bleeding. Grey colored fundus part of stomach was dissected out in a dish containing Krebs solution. By suitable transverse cuts, a strip of 4-5 cm of fundus was made and the preparation was mounted in a krebs solution at 37^0C well aerated in an organ bath tying one end of the strip to a tissue holder and the other end to isotonic fine movement transducer. 1g stretching weight was applied and the tissue was allowed to stabilize for 20 min during which time the preparation was washed every 5 min. with bath solution. The concentration dependant contractions were recorded using a single channel student physiograph. A contact time of 30 sec was allowed in a time cycle of 6 min. the concentration response curves were conducted for 5-HT and Ach in the absence and presence of SJ KIDDROPS. The percentage inhibition of the 5-HT and Ach evoked contractions by SJ KIDDROPS was calculated by considering the maximum contraction obtained as 100%. The results were expressed as arithmetic mean ± SEM. Minimum of 6 experiments were carried in each group.

Effect of SJ KIDDROPS on Intestinal transit time[9, 10].

Female albino mice (20-25g) were randomly divided into 5 groups of 6 mice each. The animals were starved for 24 hrs prior to the experiment but were allowed access to water. One group of animals was given 20 ml/kg b.wt. of normal saline orally, while remaining 3 groups received orally SJ KIDDROPS at a doses of 50, 100, 200mg/kg. The last group received atropine (0.1mg/kg). After 60 min. of drug administration through oral route (15 min after drug administration through i.p) charcoal meal (0.2 ml of a 4% suspension of charcoal in 2% carboxy methylcellulose solution) was administered to each animal orally. The animals were killed 30 min later and the abdomen was opened. Percentage distance (from pylorus to caecum) travelled by the charcoal plug in all the groups were determined.

RESULTS

Effect on guinea pig ileum:

Acetyl choline (5.5 X 10^{-8} to 176 X 10^{-8}M), Histamine (2.6 X 10^{-8} to 83.3 X 10^{-8} M), Barium chloride (2.4 X 10^{-6} to 76.8 X 10^{-6}) produced concentration dependant contraction of guinea pig ileum. SJ KIDDROPS (0.32 mg/ml of bath

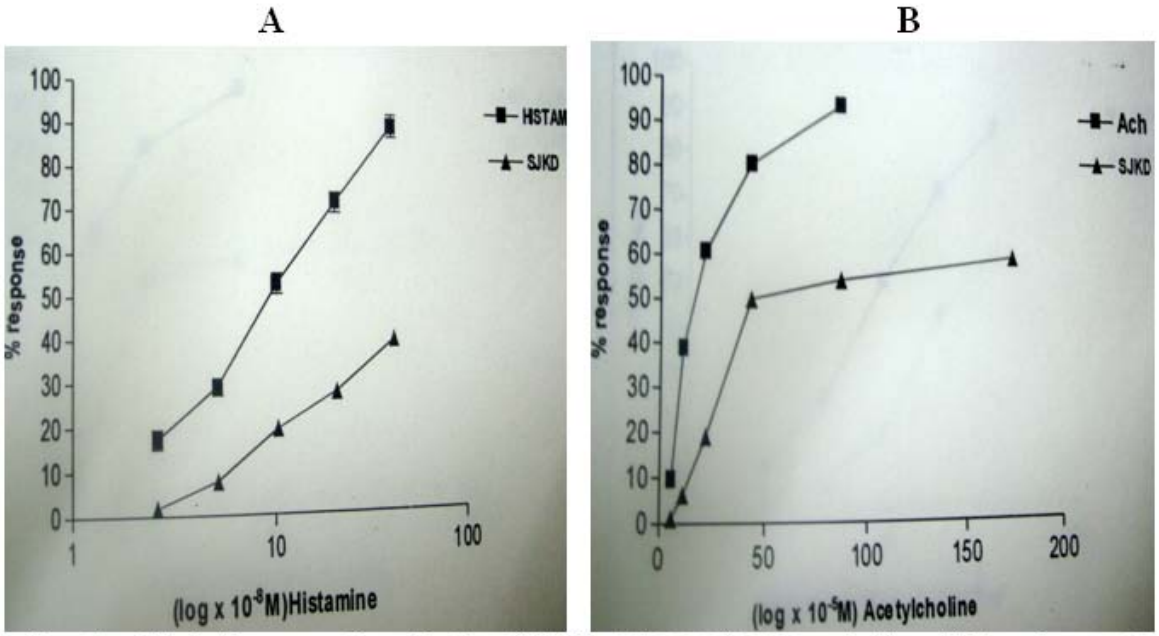

Fig. 1. (A) Antispasmodic activity of SJ KIDDROPS(0.32mg/ml) on Histamine and (B) Acetyl choline induced contractions on guinea pig ileum respectively.

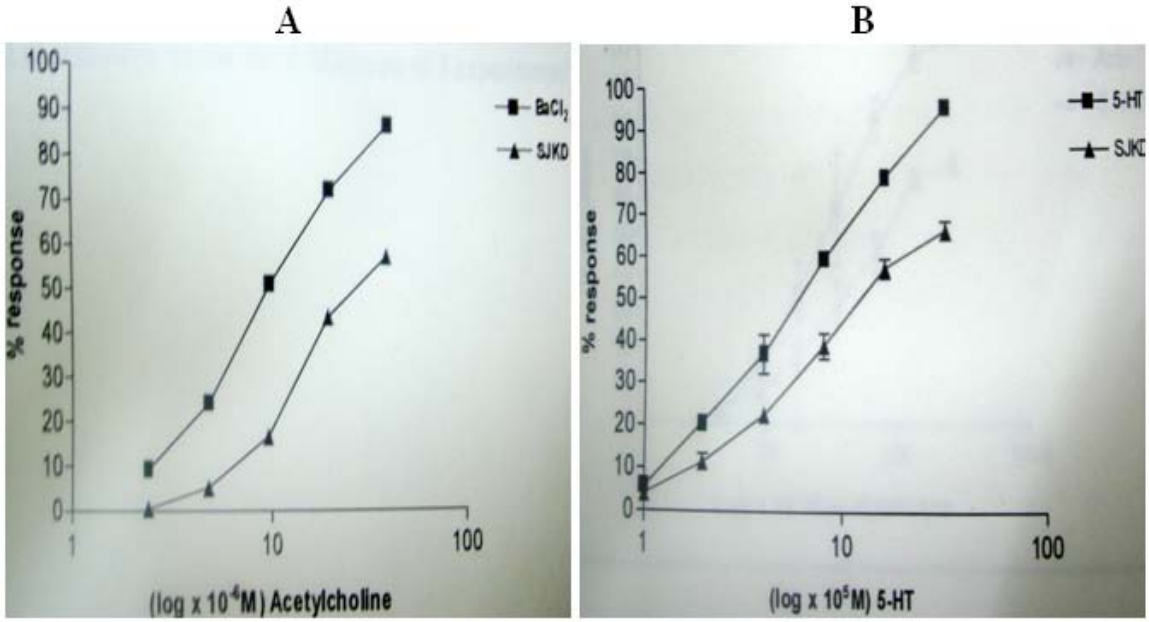

Fig.2. (A) Antispasmodic activity of SJ KIDDROPS(0.32mg/ml) on Barium chloride induced contractions on guinea pig ileum .
(B) Antispasmodic activity of SJ KIDDROPS (0.32mg/ml) on 5-HT induced contractions on rat fundus preparation.

volume) shifted the concentration response curve of acetyl choline, histamine and barium chloride to right. SJ KIDDROPS produced reversible blockade of acetyl choline, histamine and barium chloride induced spasm.

Reduction of contraction by SJ KIDDROPS was 62.3% for histamine(fig.1A), 60.11% for acetylcholine(fig.1B), and 65.92% for barium chloride(fig.2A) respectively and the dose ratio of SJ KIDDROPS on acetyl choline induced contraction was 4.25, for histamine the dose ratio was 3.35 and for barium chloride the dose ratio was found to be 1.98.

Effect on rat fundus

5-HT (1 X 10^{-5} M to 66 X 10^{-5} M) and acetyl choline (4.4 X 10^{-5} M to 280.1 X 10^{-5} M) produced concentration dependent contraction of rat fundus preparation. SJ KIDDROPS (0.32 mg/ml of bath volume) shifted the concentration response curve of acetyl choline and 5-HT to right with 75.6% and 66.75% reduction in the maximal response respectively(fig.2B). The blockade produced by SJ KIDDROPS on acetyl choline and 5-HT induced spasm was reversible. The dose ratio of SJ KIDDROPS on 5-HT induced contraction was 1.79 and 3.09 on acetylcholine induced contraction.

Effect on Intestinal transit time

SJ KIDDROPS (50-200 mg/kg b.wt.) dose dependently reduced intestinal transit time in mice. The effects on this parameter were significant at a dose of 50, 100 and 200 mg/kg b.wt. po. At 200 mg/kg po SJ KIDDROPS produced 50.87 ± 4.91% inhibition, whereas atropine at 0.1 mg/kg ip produced 36.88± 5.41% inhibition. Thus the results of charcoal meal test showed that, SJ KIDDROPS caused a significant decrease in gut motility when compared with control.

DISUSSION

According to the results the SJ KIDDROPS antagonized contractions evoked by spasmogens like Ach, histamine, 5-HT and $BaCl_2$. Further, as spasms induced by barium chloride (an agent that releases bound Ca^{2+}) were inhibited, the formulation appears also to act via the musculotropic route[11, 12], and probably inhibits smooth muscle responsiveness by interfering with Ca^{2+} availability to contractile apparatus by inhibiting the release of bound Ca^{2+} [13].

SJ KIDDROPS showed a direct action on the smooth muscles of the guinea-pig ileum and rat fundus. The antagonism against these spasmogens which have different modes of action suggests that the SJ KIDDROPS may act on the contraction mechanism. Acetylcholine, as is well known opens receptor-operated calcium channels and releases calcium from its storage sites, thus inducing phasic and tonic contractions[14]. Since the SJ KIDDROPS inhibited acetylcholine and histamine-induced spasms, it could be concluded that the SJ KIDDROPS inhibited both muscarinic and histaminic receptors. The SJ KIDDROPS possess both anticholinergic and antihistaminic properties[15]. The effect of the extract on transmitter release and receptor functions as evidenced by inhibition of contractions elicited by acetylcholine and histamine suggest a neurotropic mechanism[12, 16]. Furthermore, as barium chloride (an agent that releases bound [Ca2+]) induced spasms were also inhibited, the extract appears to be also acting by the musculotropic route[11] and probably inhibit smooth muscle responsiveness, interfering with Ca^{2+} availability to contractile apparatus by inhibiting the release boundCa2+[13, 17].

5-HT is involved in the pathogenesis of various type of secretory diarrhea including irritable bowel syndrome (IBS) rationalizes the use of SJ KIDDROPS in the management of IBS in children. The finding that SJ KIDDROPS decreased peristaltic movement in the charcoal meal study corroborated with some of the results of *invitro* studies. In conclusion, the data obtained have provided evidence to support the antispasmodic activity of SJ KIDDROPS.

CONCLUSION

All the above findings suggest that SJ KIDDROPS is a non-specific antispasmodic, which can be used in the treatment of various spasmodic disorders of gastrointestinal tract and other viscera. The present study confirms the antispasmodic activity of the said constituents

using modern Pharmacodynamic experiments. Further studies are required to find the biochemical and molecular mechanism of action of SJ KIDDROPS

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