Antispasmodics – A New Perspective

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ABSTRACT
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. Anti-spasmodics are recommended to treat acute spasmodic or colicky pain.

INTRODUCTION
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. Some are used together with antacids or other medications to treat peptic ulcer.

Anti-cholinergics/anti-spasmodics are also used in certain surgical and emergency procedures. In surgery, anti-cholinergics are given by injection before anesthesia to help relax and decrease secretions of saliva and bronchi. During anesthesia and surgery, atropine, glycopyrrolate, hyoscyamine, and scopolamine are used to help keep the heartbeat normal. Atropine is also injected to help relax the stomach and intestine for certain types of endoscopic examinations.

History and the use of Antispasmodics
- The first treatment of shula appears in the Caraka Samhita and Sushruta Samhita. Various herbs have been identified and used as antispasmodics; one of them is Apium graveolens.
- Peppermint, (Mentha piperita) is used in the treatment of colic, indigestion, irritable bowel syndrome and flatulence.
- Ginger roots are used for motion and morning sickness. It reduces intestinal cramping associated with gastro-intestinal infections and functional motility disorders.

Limitations of Antimuscarinic Antispasmodics
- Atropine – When injected into humans during pregnancy, atropine has been reported to increase the heartbeat of the fetus.
- Dicyclomine – Dicyclomine has been associated with a few cases of human birth defects.
- Hyoscyamine – When injected into humans during pregnancy, hyoscyamine has been reported to increase the heartbeat of the fetus.
- Breast-feeding – Although these drugs may pass into the breast milk, they have not been reported to cause problems in nursing babies. However, the flow of breast milk may be reduced in some patients. The use of dicyclomine in nursing mothers has been reported to cause breathing problems in infants.
Limitations of Antimuscarinic Antispasmodics in Children
Unusual excitement, nervousness, restlessness, or irritability, unusual warmth, dryness, and flushing of the skin are more likely to occur in children, 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. Shortness of breath or difficulty in breathing has been observed in children administered with dicyclomine.

Limitations of Antimuscarinic Antispasmodics in the Elderly
The following may be more likely to occur in the elderly, who are usually more sensitive than younger adults to the effects of anti-cholinergics.

Confusion or memory loss; Constipation; Difficult urination; Drowsiness; Dryness of mouth, nose, throat, or skin; Unusual excitement; Nervousness; Restlessness; Irritability.

Drug Interactions with Antispasmodics
- Antacids, antidiarrheal drugs containing kaolin or attapulgite and Ketoconazole reduce the effects of the anti-cholinergics.
- Central nervous system (CNS) depressants: Scopolamine with CNS depressants may increase the effects of either drugs.
- Tricyclic antidepressants: amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine may cause an increase in the effects of the anti-cholinergics.

Looking into the older perspectives and limitations of conventional anticholinergic, anti-spasmodics, there are needs to develop newer and safer antispasmodics for the management of broader types of spasmodic pain disorders. Anti-spasmodics are recommended to treat acute spasmodic or colicky pain.

CLASSIFICATION OF ANTISPASMODICS
Antimuscarinics (Anti-cholinergics)
1. Dicyclomine
2. Atropine
3. Hyoscine
4. Propantheline
Mebeverine and related compounds: Alverine, Drotaverine, Penavarium bromide etc.
Peppermint oil.

PAIN
- Unpleasant sensation felt in a particular part of the body.
- All tissues are innervated by nerve endings that respond to mechanical, thermal, chemical stimuli and produce increased concentration of pain modulatory factors in the inflamed tissues.
- It is a subjective correlate of tissue-protective behaviors.
- Most pains have the common mechanisms.
- Pain is associated with intense stimuli such as nausea, vomiting, headache etc.

PAIN MODULATORY FACTORS
Various chemical agents in the tissues activate primary afferent nociceptors.
These are:
- Broadykinin
COLICKY PAIN
An attack of spasmodic pain in the abdomen:
- Simple colic often results from indigestible material in the alimentary tract leading to spasmodic contractions in the muscular linings.
- Constipation with accumulation of fecal matter.
- Biliary colic: Violent/acute pain due to cholecystitis or biliary calculus or gallstones.
- Recal colic where renal calculus descends from the kidney along with ureter into the bladder.
- Uterine colic: Spasmodic contractions of the uterine smooth muscles.

Painful menstruation: More than 50 percent of women experience some discomfort during the menstrual cycle and 5-10 percent of girls in their late teens and early twenties are incapacitated for several hours each month. Severe dysmenorrhea is most prevalent in young women leading sedentary lives and its frequency has some economic importance, for the patients are often incapacitated for work for one or more days during each period.

Primary dysmenorrhea: This pain is of uterine origin and directly related to menstruation. It may be described as primary and spasmodic. Pain develops during the first day of menses when severe excruciating lower abdominal pain is experienced, lasting from half an hour to an hour. It may cause faintness; collapse and vomiting and sometimes mild degree of shock may follow. The discomfort sometimes starts on the days before menstrual flow and persists for more than 12-24 hours. It is usually cured by pregnancy.

Secondary Dysmenorrhea
It may occur at any age between puberty and menopause. It occurs in pathological conditions causing pelvic congestion. This takes the form of premenstrual pain, situated either in the back or lower abdomen, lasting between 3-5 days and sometimes even longer, and occurring before the onset of menstruation. It is always relieved by menstrual flow. It may be associated with pelvic tumors, adenoses, pelvic endometriosis, LUCD, cervical stenosis. Not all patients suffering from congestive dysmenorrhea have an organic basis to account for their pain.

Irritable bowel syndrome (IBS): It is a disorder of gastrointestinal function. Patients with IBS usually have abnormal intestinal motility. Irritable bowel syndrome patients with constipation have almost no peristaltic contractions, while patients with diarrhea have as many as 25 contractions daily. The number of peristaltic contractions is related to stool transit time. Fewer the contractions, longer the transit time. This, in turn, leads to a greater reabsorption of
water and the formation of large, hard stools. Increased peristalsis leads to a rapid transit time, less reabsorption of water and diarrhea.

Irritable bowel syndrome patients have altered visceral nociception or perception of gastrointestinal stimuli. They are very sensitive to any pressure or pain in the GI tract. The increased sensitivity can be so pronounced that even normal intestinal contractions or gas can cause discomfort or pain. Increased sensitivity to pain is referred to as visceral hypersensitivity of hyperalgesia.

Irritable bowel syndrome is characterized by persistent or recurrent abdominal, pelvic or back pain, abdominal distension and abnormal bowel movements. Some individuals suffer from diarrhea and constipation. Others have prolonged constipation followed by a bout of diarrhea. The passage of mucus in the stools is common, as is a sensation of incomplete evacuation. Diarrhea is usually worse in the morning and after meals. It has been demonstrated that the levels of serotonin or 5-hydroxytryptamine increase after meals in patients with IBS. Irritable bowel syndrome is now considered to be a functional disorder of GI tract associated with 5-HT₃ receptors in the gut.

Management of Colicky pain
1. **Pain relief**: Regardless of the cause, anti-inflammatory and more direct pain relievers are needed to relieve pain and relax the smooth muscles.
2. **Supportive therapy**: If the patient is in acute shock, appropriate treatment with fluids is essential.
3. **Specific treatment for the resolution of the cause**: This may be needed for removal of obstructive factors. Examples: Removal of calculus, fecalith, etc.

Considering pain relief as an important factor in the management of colicky pain, herbal anti-spasmodic constituting *Curcuma zedoaria*, *Zingiber officinale* and *Apium graveolens* was developed in the form of soft capsules and subjected for multicentric clinical trials. These trials included the evaluation of new herbal anti-spasmodic in patients with colicky disorders like nonspecific abdominal colic, irritable bowel syndrome, infective diarrhea, acute amoebic colitis, pain associated with lower urinary tract infection and painful menstruation.

**EVALUATION OF SJ-200 (AN HERBAL ANTISPASMODIC) IN PAINFUL MENSTRUATION**
Almost all women experience pelvic discomfort during and at the onset of menstrual flow. The precise cause of primary dysmenorrhea is not known. However, prostaglandin F₂α is involved in a large number of patients. Normal uterine contractions become stronger and stronger just before the onset of and during menstruation, which produce spasmodic and colicky pain especially in the lower abdomen. Conventionally NSAIDs, which suppress prostaglandin synthesis, are used for symptomatic relief. However, most of the NSAIDs produce gastrointestinal discomfort and are not suitable for long-term use.

**MATERIAL AND METHODS**
Forty young females between the age of 25 and 30 who had moderate to severe spasmodic dysmenorrhea were selected for the study. All of them were screened completely to rule out
endocrine and reproductive abnormalities associated with dysmenorrhea. All the patients were administered 2 capsules of SJ-200 during the attack of acute pain. Subsequently, if the pain was not relieved, 1 capsule of SJ-200 was repeated after 1 hour of the first dose. Further, all of them had a maintenance dose of SJ-200 of 1 capsule thrice daily for the next 2 days.

RESULTS
A significant number of patients showed reduced intensity of pain and subsequently complete relief. A majority of patients experienced a disappearance of pelvic heaviness after taking SJ-200. By maintaining the use of SJ-200 during 3-4 menstrual cycles, it was observed that the severity of menstrual cramps reduces significantly during subsequent cycles.

In vitro experimental model of rat uterus has demonstrated the inhibition of prostaglandin F\textsubscript{2a}-induced uterine contractions by SJ-200 in a dose-dependant manner. The findings confirm a similar pharmacodynamic activity of SJ-200 in patients with primary spasmodic dysmenorrhea. Thus, SJ-200 is a suitable and safe anti-spasmodic for the relief of spasmodic dysmenorrhea.

MECHANISM OF ACTION
Contraction in smooth muscle, mediated by interactions between actin filaments and cross-bridges on adjacent myosin filaments, is triggered by the rise in cytoplasmic calcium and consequent phosphorylation of the 20 kDa light chains of myosin. The cross-bridges are the motors that utilize ATP as an energy source for the generation of force and work.

The increase in Ca\textsuperscript{2+} has many consequences:

1. Activation of protein kinase such as Protein kinase A, Protein kinase C\textgreek{g}
2. Calcium-calmodulin activated kinase II
3. Mice lacking PKC\textgreek{g} or CAMK-II show reduce hyperalgesia in nerve inflammatory pain
4. Activation of nitric oxide synthase (NOS)
5. Activation of cyclo-oxygenase 2 (Cox-2)
6. Increase intracellular Na\textsuperscript{+} activates tyrosine kinase.

The experimental evidences prove that SJ-200 produces anti-spasmodic action by the following mechanisms:

- SJ-200 has no agonistic activity on specific receptors like muscarinic, histaminergic, oxytocin, 5-HT and PGs.
- SJ-200 inhibits the contractions produced by various spasmogens like acetylcholine, barium chloride, histamine and oxytocin. This suggests that the activity of SJ-200 is non-specific to any spasmogen. Thus it acts like a non-specific antispasmodic pain reliever.
- The various spasmogens have different models of action in producing contractions of smooth muscles, the antagonism elicited by SJ-200 indicates that it acts at a common site in the contractile process, i.e., the influx of calcium at plasmalemma.
MECHANISM OF ACTION IN IRRITABLE BOWEL SYNDROME

- SJ-200 decreases gastric emptying and intestinal transit. This indicates the inhibition of increased gastrointestinal motility.
- The inhibition of spontaneous and agonist-induced contractions also confirms the inhibition of the gastrointestinal motility. This pharmacological property is useful in the management of non-specific diarrhea as well as IBS.
- Inhibits serotonin-induced contractions. Serotonin levels are increased in patients with IBS especially after meals.

USES OF SJ-200

- Relieves spasmodic pain in uterus
  - Spasmodic dysmenorrhea
  - Menstrual cramps
- Cures abdominal colic
  - Intestinal colic (amoebic colitis)
  - Fecal obstruction
  - Irritable bowel syndrome
  - Cholecystitis and gallstones
  - Parasitic obstruction
- Treats non-specific diarrheas
  - Chronic infective and secretory diarrheas
- Helpful in others
  - Ureteric spasms
  - Acute pain associated with lower UTI
  - Acute pain due to calculus

CONCLUSION

Looking into the perspectives and uses of conventional antimuscarinic-antispasmodics, SJ-200 confirms the efficacy and safety when used for the treatment of various spasmodic disorders in the recommended dosage. The recommended duration of treatment should follow for minimum 3-5 days. However in patients with irritable bowel syndrome and secretory diarrhea, the duration of treatment may be prolonged for 4-6 weeks.

BIOBIBLIOGRAPHY