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Research Article

A New Sorbent Based on Polymethylsilsesquioxane-Zinc Effectively Inhibits the Contractile Activity of Guinea Pig *Taenia coli*

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Abstract

A Polymethylsilsesquioxane-zinc™ sorbent (PSS-Zn) is capable of dose-dependently inhibiting spontaneous autorhythmic activity and dose-dependently relaxing isolated segments of guinea pig *Taenia coli*, pre-activated with a high concentration of potassium chloride. This effect can be considered a manifestation of PSS-Zn's potential antidiarrheal properties. The relaxing effect of the dimethyl sulfoxide (DMSO) solvent on *Taenia coli* segments was insignificant at all doses, except for the maximum solvent concentration of 1 mg/ml. Thus, it can be concluded that it is the PSS-Zn sample itself, and not its DMSO solvent, that exerts the antidiarrheal (relaxing) effect. When the PSS-Zn sample was added to the tissue bathp solution simultaneously with acetylcholine, an increase, rather than a decrease, in *Taenia coli* smooth muscle activity was observed. Therefore, it can be assumed that the antidiarrheal (dilating) properties of PSS-Zn are not related to its effect on acetylcholine receptors. Given that PSS-Zn is capable of relaxing *Taenia coli* segments previously constricted by a potassium chloride solution (60 mmol), the relaxing effect of the studied PSS-Zn samples is likely due to blockade of calcium ion entry through voltage-gated calcium channels or its direct calcium-binding action.

Keywords: *Taenia coli; Diarrhea; Smooth Muscle Contractile Activity; Polymethylsilsesquioxane-Zinc™-Based Sorbent*

Introduction

Diarrhea (loose stools) is a common and clinically significant condition characterized by frequent, loose stools. It is a symptom of various diseases and conditions, from mild eating disorders to very serious and dangerous infectious and/or inflammatory bowel diseases. The greatest, and often fatal, dangers associated with diarrhea are dehydration and the loss of vital electrolytes - potassium, sodium, and magnesium. This leads to serious complications, especially in children, the elderly, and those with weakened immune system.

Clearly, all of this taken together has necessitated the development of new effective antidiarrheal medications. Typically, diarrhea is treated with medications that either reduce gastrointestinal motility or increase stool volume by, for example, increasing water content. The most commonly used modern antidiarrheal medications, which aim to reduce intestinal motility, unfortunately, often have side effects due to their mechanism of action.

It is well known that colonic motility depends largely on the activity of one of the components of the intestinal wall, *Taenia coli*, a type of tapeworm with autorhythmic activity. *Taenia coli* are three longitudinal bands of smooth muscle that run along the colon and are slightly shorter than it. This leads to the formation of folded protrusions called haustra. These structures play an important role in the compaction of faecal matter; their contraction promotes colonic peristalsis and the propulsion of faeces.

Thus, the haustra facilitate the slow movement of intestinal contents, ensuring better absorption of water and nutrients. This ultimately promotes mixing and compaction of the semi-liquid stool within the haustra pouches. The contents of one haustra pouch then move to the next section, where another pouch is formed, and from there to the next segment, where the process repeats. All this promotes the slow, progressive movement of intestinal contents and compaction of stool in the colon.

During diarrhea, colon motility increases, meaning it contracts more strongly and more frequently than usual. As a result, the aforementioned "haustration" of faeces does not occur, which is accompanied by corresponding clinical symptoms. These include increased stool frequency, the appearance of loose stools, abdominal cramping, and so on.

Thus, based on current understanding of colon physiology, a drug capable of inhibiting *Taenia coli* activity should exhibit significant antidiarrheal activity. The development of a drug capable of simultaneously inhibiting smooth muscle activity and absorbing protein or polysaccharide toxins that cause infectious diarrhea would mark a new era in the treatment of diarrheal syndrome. New oral intestinal adsorbents offer an alternative to known antidiarrheal drugs for the safe and effective treatment of acute diarrhea of infectious and non-infectious etiologies in children aged 1 year and older [1].

For example, data have been obtained on the positive results of using intestinal absorbent based on polymethylsiloxane polyhydrate for the treatment of diarrhea in vulnerable population groups [3].

Aim of the Study

The aim of this study was to study the effect of a new Polymethylsilsesquioxane-zinc™-based sorbent on the spontaneous and induced contractile activity of *Taenia coli*.

Materials and Methods

Ethical approval and animals

All animal studies were performed in accordance with the recommendations of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes and approved by the Institutional Animal Care and Use Committees.

Experiments were performed on male Guinea pigs (weight 210 - 300g) housed under controlled environmental conditions (21°C, 2h - 12h light-dark cycle) and free access to water and standard rodent chow.

The animals were anesthetized with alpha-chloralose (40 mg/kg) and urethane (400 mg/kg body weight, intraperitoneally), and then killed by displacement of the cervical vertebrae.

Method of recording contractile activity of isolated segments of the guinea pig colon (*Taenia coli*)

Taenia coli segments were prepared and cleaned of connective and fatty tissues in modified Tyrode's solution with the following composition (in mM): NaCl 133, KCl 4.7, $NaHCO_3$ 16.3, NaH_2PO_4 1.38, $CaCl_2$ 2.5, (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) 10, D-glucose 7.8 (pH adjusted to 7.4 with NaOH).

Taenia coli segments were placed in a 1 ml organ bath with a flowing buffer solution, where they were fixed on two steel hooks, one of which was permanently mounted to the chamber wall, and the other connected to the strain gauge rod. To obtain the optimal contraction force, *Taenia coli* segments were subjected to preliminary passive stretching with a force of 500 - 900 mg.

Registration of contractile activity of isolated *Taenia coli* segments was carried out using an isometric force transducer (AE 801, SensoNor, A/S, Norten, Norway) coupled to an AD converter Lab-Trax-4/16 (World Precision Instruments, Inc., Sarasota, USA. The signal from the isometric tension sensor was transmitted to the input of a differential amplifier and recorded using an analogue-to-digital converter Labtrax 4/16 and Labscribe 2 software (World Precession Instrument Inc., USA).

Taenia coli segments in the chamber were perfused with Tyrode buffer solution at a constant rate of 2.5 ml/min using a 4-channel peristaltic pump IPS ISM 930 "Ismatec" (Germany) at a temperature of 37°C. Applications of the studied concentrations of the test sample "PSS-Zn" were carried out using a perfusion system.

Analysis and statistical processing of the obtained results

Statistical analysis of the data was performed using Student's unpaired t-test. The data are shown as means ± SEM; n indicates the number of vascular preparations or cells tested. The comparison of the obtained values was carried out using the parametric Student's t-test for unpaired measurements. Differences were considered statistically significant if the P value was less than 0.05. All calculations were performed on a personal computer using the OriginPro 2021 programs (Microcal Software Inc., OriginLab Corporation, USA) and Microsoft Excel 5.0 (Microsoft, USA).

The values of the average effective concentrations of the test sample are presented as the negative logarithm of the concentration required to develop a half-maximal response (pD_2). The calculation of this parameter was carried out using the OriginPro 2021 program (OriginLab Corporation, USA), which is based on the following formula:

$$T = \frac{100}{1 + 10^{Log(x0 - x) \bullet p}}$$

Where, T is the normalized tone level (expressed as a percentage of the initial drug reduction level) at the concentration of the test substance x (expressed as a negative logarithm); X_0 is the midpoint of the dose-response curve (i.e. T = 50%) and p is the slope of the curve. The final pD_2 values were obtained by averaging the pD_2 calculated separately for each *Taenia coli* segment.

Results

We have studied the effect of the following doses of the compound Polymethylsilsesquioxane-zinc™ sorbent (PSS-Zn: 0.1 mg/ml, 0.2 mg/ml, 0.5 mg/ml and 1 mg/ml on the contractile activity of guinea pig *Taenia coli*. It was shown that a dose-dependent decrease in the amplitude of phasic contractions of *Taenia coli* under the influence of the studied sorbent sample was observed starting from a concentration of (0.1 mg/ml) mol/l. At the same time, the frequency of contractions remained virtually unchanged.

The most pronounced effect was observed at a concentration of 0.5 mg/ml. In this case, the amplitude of the phase contractions and, consequently, the isometric tension (tone) developed by *Taenia coli* at the maximum applied concentration of the compound "Polymethylsilsesquioxane-zinc™" (1 mg/ml) fell more than twofold. It was on average, 41.5 ± 3.3% of the value of contraction of *Taenia coli* segments in the control, i.e. before exposure to the studied sample ($p < 0.05$, $n = 15$). It was established that the average effective concentration of the "Polymethylsilsesquioxane-zinc™" sample (pD_2) was - 2.1 ± 0.01) (Figure 1).

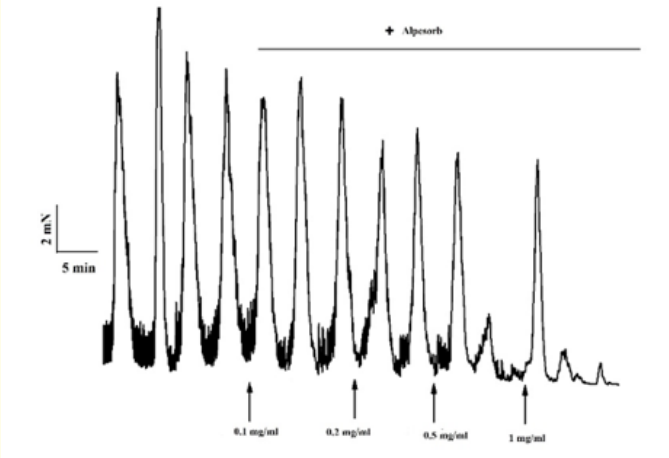

Figure 1: *Original recording of spontaneous contractile activity of segments of guinea pig Taenia coli under the influence of different doses of the test sample PSS-Zn: 0.1 mg/ml), 0.2 mg/ml, 0.5 mg/ml, 1 mg/ml.*

The effect of DMSO itself on the relaxing activity of *Taenia coli* preactivated with high-potassium solution was tested separately (See below in figure 4). Figure 2 and 3 represent dose-dependent effect of "PSS-Zn" on tonic tension of *Taenia coli* preactivated with 60 mM KCl.

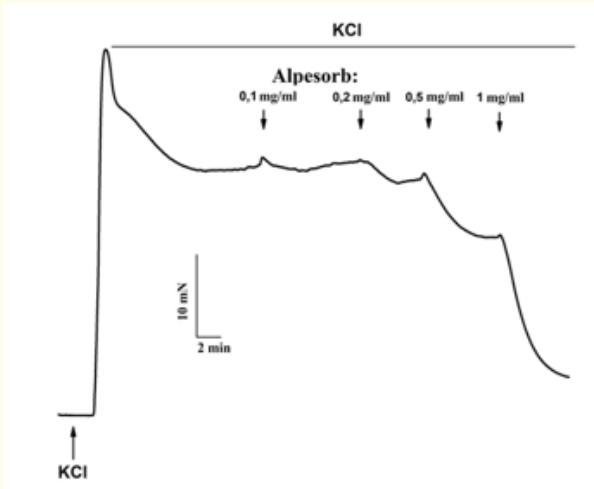

Figure 2: *Recording of the effect of the test sample PSS-Zn in doses: (0.1 mg/ml), (0.2 mg/ml), (0.5 mg/ml), (1 mg/ml) on the contractile activity of guinea pig Taenia coli segments against the background of KCl (60 mmol) action.*

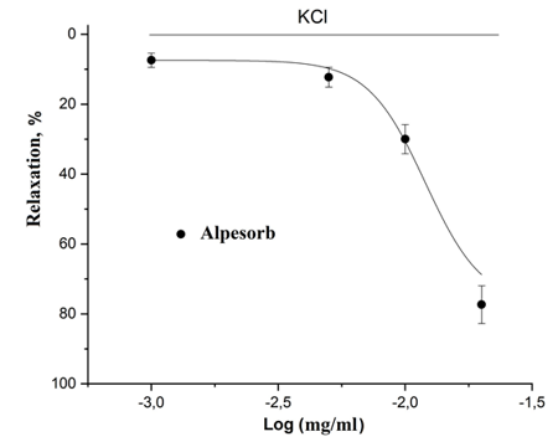

Figure 3: *Dose-effect curves of the dilator effect of the test sample PSS-Znon segments of guinea pig Taenia coli pre-activated with KCl (60 mmol).*

The samples of "Polymethylsilsesquioxane-zinc™" (PSS-Zn) was previously dissolved in dimethyl sulfoxide (DMSO), which is a solvent of low toxicity, which, however, in high concentrations is able to show activity and significantly change the contractility of smooth muscles [2]. Therefore, it seemed appropriate to separately determine the effect of DMSO on the tone of *Taenia coli* segments in order to compare it with the effect of the combined action of DMSO and the test sample of "Polymethylsilsesquioxane-zinc™" dissolved in it.

It is clear that DMSO in its pure form has dilatatory activity, but to a significantly lesser degree than in combination with the studied sorbent sample (Figure 4). Thus, the results obtained indicate that the test sample of sorbent is capable of causing dose-dependent relaxation of isolated segments of *Taenia coli*, which can be considered a manifestation of its antidiarrheal properties.

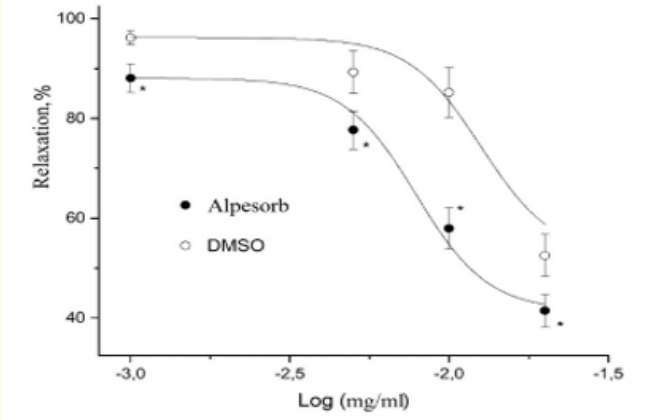

Figure 4: *Dose-effect curves of the relaxing effect of the test sample PSS-Zn in comparison with its solvent (DMSO) on segments of guinea pig Taenia coli. - P<0.05 - compared with DMSO.*

Acetylcholine (ACh) plays a key role in the contraction of the *Taenia coli* smooth muscle. Specifically, ACh increases the muscle's tone by increasing the permeability of cell membranes to calcium ions, leading to depolarization and increased action potential frequency. This process involves multiple components, including increased calcium entry, release of membrane calcium, and a "spike mechanism" that ultimately results in muscle contraction.

When acetylcholine binds to receptors on the *Taenia coli* muscle cells, it triggers a cascade of events. One key event is the release of calcium ions from intracellular stores and an increase in the influx of calcium ions from the extracellular space [4].

A possible mechanism of the inhibitory effect of the sorbent on the phase activity of *Taenia coli* could be the blocking of the cholinergic regulation mechanism. Therefore, in order to establish possible mechanisms of the dilating antidiarrheal action of the studied sample "Polymethylsilsesquioxane-zinc™", segments of guinea pig *Taenia coli* were exposed to increasing doses of the sorbent in combination with acetylcholine.

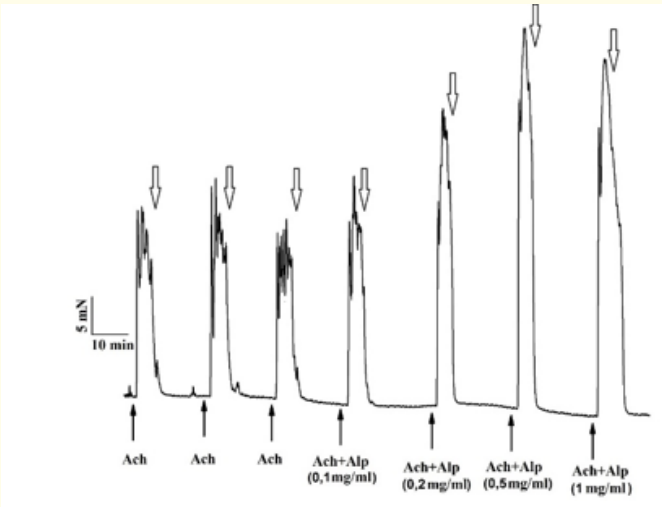

Figure 5: *Fragment of the recording of the contractile activity of segments of guinea pig Taenia coli under the influence of acetylcholine (Ach) alone and Ach and different doses of the test sample PSS-Zn (Ach+ALP): (0.1 mg/ml), (0.2 mg/ml), (0.5 mg/ml), (1 mg/ml).*

Discussion

Sorbents, also known as entertosorbents, are substances that can bind to toxins and other substances in the digestive tract, helping to relieve diarrhea. They work by adsorbing, or binding, to these substances on their large surface area, and then the sorbent, along with the adsorbed substances, is eliminated from the body. While they can be helpful in managing diarrhea, it's important to note that they may not be effective for all causes of diarrhea and can sometimes cause constipation.

Analysis of the results of screening studies of the provided test sample of the medical product based on PSS-Zn showed that it is able to significantly affect spontaneous activity of *Taenia coli* segments, causing their dose-dependent relaxation (Figure 1). It is important to note that PSS-Zn relaxed *Taenia coli* preconstructed with high-potassium solution, indicating that this effect is due to its ability to decrease the calcium entry (Figure 2 and 3).

The data obtained showed that DMSO in concentrations corresponding to: (0.1 mg/ml), (0.2 mg/ml) and (0.5 mg/ml), did not significantly affect the contractility of the colon. However, when adding to the solution a volume of DMSO corresponding to the concentration of " Polymethylsilsesquioxane-zinc™" (1 mg/ml), a significant relaxing effect was observed, which, however, was probably less than the effect of the sorbent sample at the same concentration (Figure 4).

The obtained data on the effect of the sorbent on *Taenia coli* against the background of stimulation with acetylcholine clearly indicate that the implementation of the relaxing effect of PSS-Zn occurs without the participation of the cholinergic mechanism (Figure 5).

Considering the structure of the sorbent, it is possible to assume that its relaxing action may be associated with the chelating effect on calcium ions in buffer solution, which leads to a decrease in their activating effect on myofilaments, which requires additional research.

Conclusion

1. It has been established that the sorbent based on "Polymethylsilsesquioxane-zinc™" has sufficient ability to dose-dependently relax the smooth muscles of the *Taenia coli*, which suppresses their phase activity and inhibits peristalsis of the large intestine.
2. The relaxing effect of the sorbent is not associated with its effect on elements of the parasympathetic nervous system (intramural ganglia) and inhibition of the release of acetylcholine.
3. It is likely that the relaxing effect of the sorbent is associated with its ability to chelate calcium ions in a buffer solution and, accordingly, reduce the entry of calcium ions into muscle cells.

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