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Smooth Muscle Motility: Comparing the Effect of a Synthetic Anti-Diarrhoeal Drug with a Probiotic on an Isolated Rabbit Intestine

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***Abstract*— Background: Diarrhoea exerts an enormous toll in terms of mortality, morbidity, social inconvenience, loss of work productivity, and consumption of medical resources. Acute infectious diarrhea remains one of the most common causes of mortality in developing countries, particularly among children, accounting for 2-3 million deaths per year.**

Aim: To compare the contractile effect of a synthetic anti-spasmotic and a probiotic drug on an isolated rabbit intestine.

Method: A healthy rabbit weighing 300g was humanely sacrificed and a length of a small intestine (ileum) was isolated and submerged in a tissue bath. The test solutions (Saccharomyces boulardii, Synthetic anti-spasmodic) were then applied in graded doses and the final bath concentration calculated.

Results: The experimental data was analyzed using T-test of Independent variable and the output clearly revealed that there was no significant difference (p = 0.73) in the Amplitude between the two drugs. But there was a significant difference observed in the frequency between the two drugs (p = 0.002).

Conclusion: S. boulardii is a well tolerated probiotic with little or no side effects that has some effect on intestinal motility.

***Index Terms*— Diarrhoea, Synthetic anti-spasmodic (Loperamide), Saccharomyces boulardii, Rabbit, Ileum**

I. INTRODUCTION

Diarrhoea is defined as passage of abnormally liquid or unformed stools at an increased frequency.Diarrhoea exerts an enormous toll in terms of mortality, morbidity, social inconvenience, loss of work productivity, and consumption of medical resources. Worldwide, more than one billion individuals suffer one or more episodes of acute diarrhea each year. Among the 100million persons affected annually by acute diarrhea in the United States, nearly half must restrict activities, 10% consult Physicians, approximately 250,000 require hospitalization, and approximately 5000 die (primarily the elderly). The annual economic burden to society may exceed $20 billion. Acute infectious diarrhea remains one of the most common causes of mortality in developing countries, particularly among children, accounting for 2-3 million deaths per year (Harrison's Principle of internal medicine, 17th edition, 2008).

Diarrhoearesults from an imbalance between secretion and re-absorption of fluid and electrolytes; it has numerous causes, including infections with enteric organisms, inflammatory bowel disease and nutrient mal-absorption due to disease (Bennett and Brown 2003).Motility patterns in the bowel is an important factor in diarrhoea may be caused by loss of the normal segmenting contractions that delay passage of contents, so that an occasional peristaltic wave has a greater propulsive effect. Segmental contractions of the smooth muscle in the bowel mix the intestinal contents. Patients with diarrhoea commonly have less spontaneous segmenting activity in the sigmoid colon than do people with normal bowel habit and patients with constipation have more. Anti-motility drugs reduce diarrhoea by increasing segmentation and inhibiting peristalsis, e.g., Loperamide(Bennett and Brown 2003).

Loperamide is a derivative of meperidine. It exerts its anti-motility action through binding to opioid receptors in the intestine as well as inhibiting calcium channels and calmodulin in intestinal smooth muscle. In addition, it inhibits fluid secretion by the colonic epithelial cells. Because of its limited oral bioavailability and poor penetration across the blood-brain barrier, loperamide is a good anti-diarrheal agent with minimal side effects, especially central nervous system-related effects (Lingtak-Neander 2008).

Saccharomycesboulardii is a tropical strain of yeast first isolated from lychee andmangosteen fruits in1923 by French scientist HenriBoulard. It is related to, but distinct from, saccharomyces cerevisiae in several taxonomic, metabolic and genetic properties (Malgoireet al., 2005). S. boulardii is sometimes used as a probiotic with the purpose of introducing beneficial active cultures into the large and small intestine, as well as conferring protection against pathogenic microorganisms in the Host (Rajkowskaet al., 2012).

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However, in immuno-compromised individuals, S.boulardiihas been associated with (fungemia) or localized infection, which may be fatal(Santino et al.,2014).

While the mechanisms by which probiotics exert their benefit are not fully understood, it has been suggested that they improve host barrier function, produce competitive inhibition of pathogenic bacteria, and bolster immune function. S. boulardii secretes enzymatic proteins, including a protease that degrades clostridium difficile toxins and a phosphatase that inactivates endotoxins such as the lipopolysaccharide produced by E.Coli. It also strengthens tight junctions between enterocytes (reducing secretory IgA) (Marcia 2009).

II. MATERIALS/METHOD

The animal (Healthy Rabbit, male, 300g) was purchased and housed at the University of Jos animal house under humane conditionin line with the Helsinki declaration, ethical clearance was sought and gotten from the animal house ethical committee. The rabbit was humanely sacrificed and a length of a small intestine (ileum) was isolated, washed and placed into the petri dish containing tyrodesolution (370c), with air bubbled through the aerator (to keep the tissue alive). The isolated segment of the intestine was tied with a thread at each end and suspended into the tissue bath and the other end tied to the writing lever, the tissue was allowed to acclimatize within the new environment for 15 minutes. A spontaneous rhythmic contraction was noted, the kymograph speed was set at 0.25mm/sec, and the normal spontaneous contraction was recorded for 2 minutes. The test solutions (Saccharomyces boulardii, Loperamide hydrochloride) were then added. The tissue was washed 2-3 times until it recovered from the effect of the last test solution and a normal tracing is recorded before the next test solution was applied into the organ bath.A sufficient time of about 3-4 minutes was allowed for each test solution to penetrate the tissue; the test solutions were prepared in graded concentrations using x 10dilution and the final bath concentration was calculated using the formula $\frac{C2xV2}{C1}$ = v1

Where: C1 = stock (concentration of drugs), C2 = required final bath concentration of drugs, V1 = volume of drugs used, V2 = volume of tissue bath

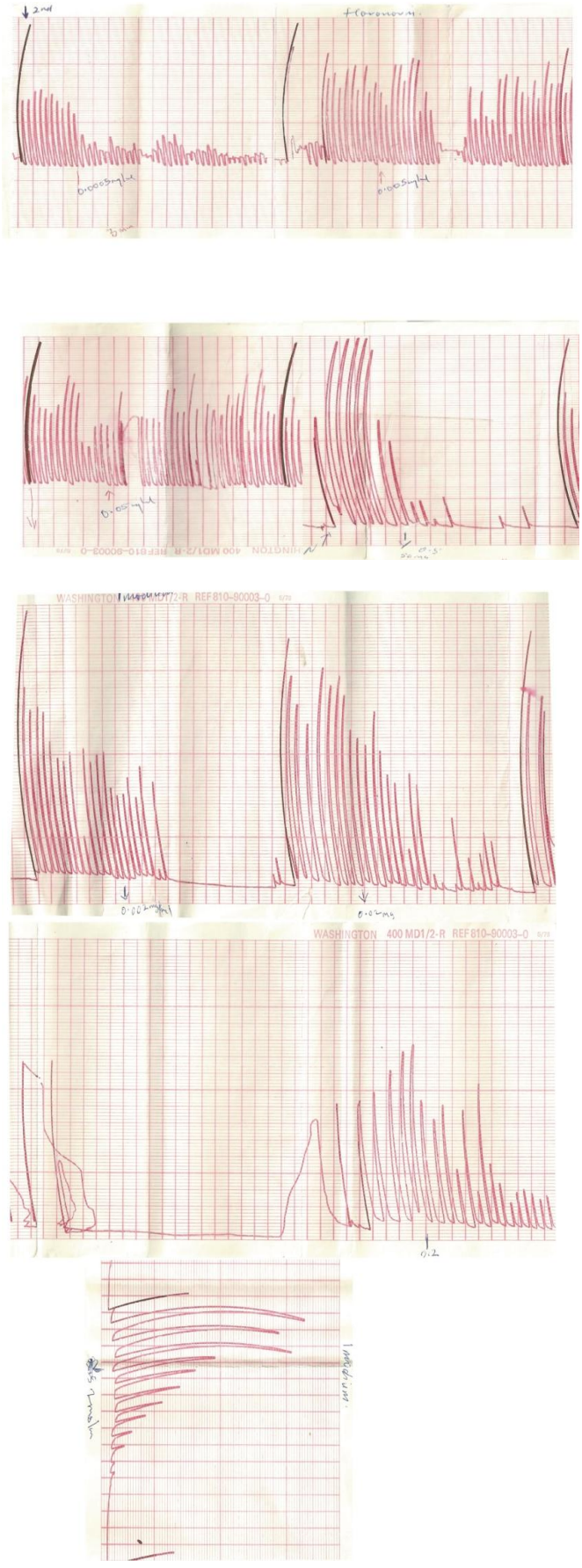
Saccharomyces boulardii; (0.0005, 0.005, 0.05 and0.5) mg/ml

Loperamide hydrochloride; (0.002, 0.02, 0.2and 2) mg/ml.

III. RESULTS

The experimental data was analyzed using T-test of Independent variable and the output clearly revealed no significant difference (p = 0.73) in the Amplitude between the two drugs. However a significant difference was clearly observed in the frequency between the two drugs (p= 0.002).

Plate: below is the tracing from the contraction of the rabbit intestine (ileum) following the application of the test solution and different concentrations;



A. Amplitude

There was no significant mean difference in amplitude between Probiotic and the synthetic anti-spasmodic drug.

Table 1: Shows the Mean amplitude Difference between Probiotic and Synthetic anti-spasmodic drug .

Drug	N	Mean	Sig. (2 tailed)
Probiotic	**4**	**20.4**	**0.73**
Synthetic drug	**4**	**17.8**	

P> 0.05

The result in Table 1 shows that there is no statistically significantmean difference in amplitude between Probiotic and the Synthetic anti-spasmodic drug (t6= 0.362, p > 0.05). However, Despite the no statistically significance in the effectiveness of the two drugs, the result indicate that the Probiotic have a higher mean amplitude effectiveness of 20.4 than the synthetic anti-spasmodic drug which mean amplitude is 17.8.

B. Frequency

There is a significant mean difference in frequency between Probiotic and the synthetic anti-spasmodic drug.

Table 2: Shows the Mean frequency Difference between Probiotic and Synthetic anti-spasmodic drug.

Drug	N	Mean	Sig. (2 tailed)
Probiotic	**4**	**9**	**0.002**
Synthetic drug	**4**	**4.5**	

P <0.05

The result in Table 2 shows a statistically significant mean difference in frequency between Probiotic and the Synthetic anti-spasmodic drug. (t6= 5.362, p < 0.05). In other words, the probiotic drug has a statistically significant higher average frequency of 9 than the Synthetic anti-spasmodic drug with a mean frequency of 4.5.

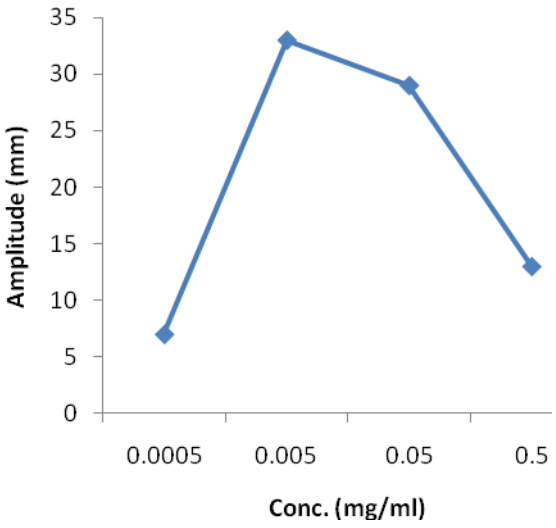


Figure 1a: Showing Amplitude of Probiotic at final bath concentration of the test solution

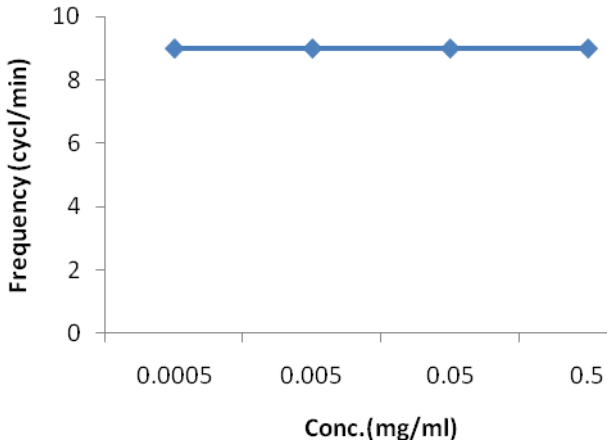


Figure 1b: Showing frequency of Probiotic at final bath concentration of the test solution

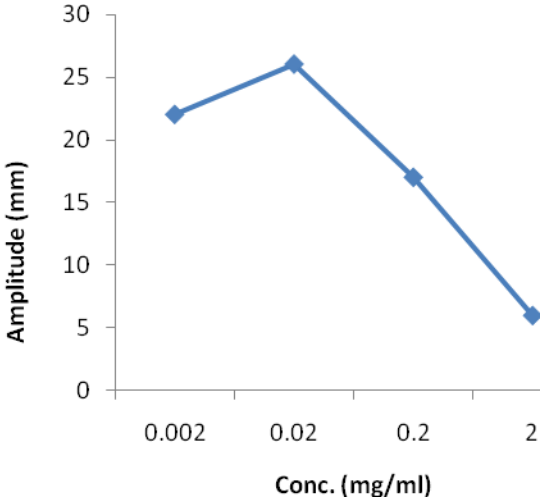


Figure 2a: Showing Amplitude of Imodium at final bath concentration of the test solution

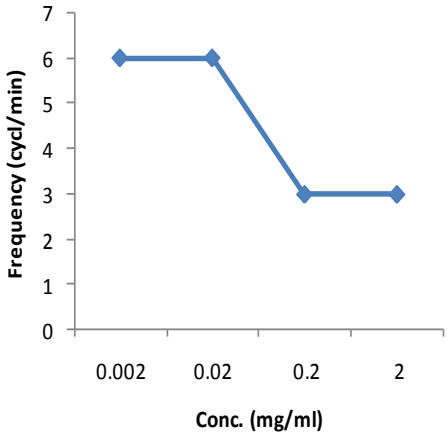


Figure 2b: Showing frequency of Imodium at final bath concentration of the test solution

IV. DISCUSSION

Our study compares the action of a synthetic

Opiodanti-spasmodic anda probiotic (Saccharomyces bolardii) on the motility of an isolated segment of a rabbit intestine. The result revealed no significant difference ($p < 0.73$) in the amplitude between the two drugs. The probiotic reduces the amplitude of the rabbits smooth intestinal muscle(figure 1) at very low concentration (0.005mg/ml) and at high concentration (0.5mg/ml), while the synthetic anti-spasmodic drug does same at a concentration of 0.02mg/ml. A significant difference ($P < 0.002$) was clearly observed in the frequency between the two drugs as stated.In a study by Micklefield on Saccharomycesboulardii in the treatment and prevention of antibiotic-associated diarrhea (AAD), in 14 out of 17 studies including 4,627 patients the administration of S. boulardii achieved a protective effect between 43.7% and 87.3% (Micklefield; 2014). The use of anti-motility drugs in diarrhoea in children (less than 4 years) is discouragedor in patients with active anti-inflammatory bowel disease, for there is danger of causing paralytic ileus and, in babies, respiratory depression (Bennett and Brown; 2003). In another study by Dinleyiciet al., on Saccharomyces boulardiiCNCM 1-745 in different clinical conditions S. boulardii is shown to be one of the best-studied probiotics in acute gastroenteritis (AGE) and is shown to be safe and to reduce the duration of diarrhoea and hospitalization by about 1 day (Dinleyiciet al.,2014). There a dart of research data on the use of S. boulardii on smooth muscle motility. However, our work showed that it has some effect at very low concentrations only, while the synthetic anti-spasmodic drug has a maximal anti-motility effect at all concentration used.

In conclusion, diarrhoeal disease contributes not only to morbidity and mortality in the world but also to school and work absenteeism with negative impact on productivity. S. boulardii is a well tolerated probiotic anti-diarrhoeal drug with little or no side effects that has some effect on intestinal motility. Thus, an effective and well tolerated anti-diarrhoeal drug will reduce morbidity and mortality.

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