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Article

Synergistic Effect of Racecadotril and Loperamide by Gastrointestinal Motility Test

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A B S T R A C T

The purpose of the study is to implicit spectacular effects of drug synergism, when two similarly mimicking drugs are administered concomitantly the effects are satisfying for the therapeutic effect expected. In this study two market available drugs Racecadotril and Loperamide were used in albino rat using Gastrointestinal Motility test as antidiarrheal screening model for studying the effects of these two drugs against diarrhoea synergistically. The results were quite satisfactorily achieved as per anticipation, further models can be used to confirm the same and also this might be the prerequisite for further development of a formulation in future.

Keywords: Synergism, Drug Synergism, Anti-diarrheal Activity, Albino Rats, Concomitantly, Synergistically

Introduction

Synergism (Greek: Syn-together; ergon-work), When the action of one drug is facilitated or increased by the other, that is what called synergistic effect. In a synergistic pair of drugs, both the drugs can have action in the same direction or given alone one may be inactive but still enhance the action of the other drug when given together.

Synergism can Either of Two Types

Additive

The effect of the two drugs is in the same direction and simply adds up:

effect of drug A + effect of drug B = effect of drug A + effect of drug B.

Examples

Amlodipine + atenolol = antihypertensive action (Marketed as Amlokind-AT tablet) Aspirin + paracetamol = enhanced analgesic/ antipyretic activity (Marketed as Diapyrin tablet)

Potentiation (Supraadditive)

The effect of combination is greater than the individual effects of the components: effect of drug A + effect of drug B > effect of drug A + effect of drug B Enalapril+ Hydrochlorothiazide (Marketed as Envas H tablet) Sulfamethoxazole + Trimethoprim (Marketed as Bactrim DS tablet).

Note: It doesn't mean always both the drugs given synergistically need to work, they may a chance where one doesn't work at all but impacts on the working of the other drug.[1]

Diarrhoea

It is defined as increase in the daily stool weight above 200 g, i.e. it usually accounts for an increase in defecation frequency and stool liquidity. Diarrhoea is referred to as acute when it lasts less than 1 to 2 weeks, whereas chronic diarrhoea lasts for a period of more than 2 to 3 weeks.[2]

The common causes of diarrhoea encountered in clinical

practice are disorders of gastrointestinal function (or irritable bowel syndrome), IBD and when associated with features suggestive of pancreatic insufficiency, celiac disease, and small bowel bacterial overgrowth. Thus, it's very important for clinician to search for these suggestive features of these diseases.[3]

Epidemiology

Diarrhoea is very common condition. In 2004 there were nearly 2.5 billion cases of diarrhoea worldwide. For children under 5 years of age, diarrhoea denotes great significance, being the second leading cause of death (after pneumonia), killing more and more young children than AIDS, malaria, and measles combined. Nearly one in five childhood deaths - about 1.5 million each year - are caused due to diarrhoea. Majority of deaths occur in Africa and Asia (Diarrhoea, 2009). Chronic diarrhoea (which lasts more than 4 weeks) however afflicts about 5% of our population, crucially impacting quality of life and representing an important cause of morbidity and mortality.[4]

Pathophysiology

Diarrhoea is the consequence of a disruption in the delicate balance between the absorptive and secretory processes within the bowel. In general, diarrhoea can be either osmotic or secretory.[5] Diarrhoea is caused due to either decreased absorption of water or increased secretion into the colon or small intestine. It might result as a result of deranged electrolyte transport or due to the presence of non- absorbable solutes in the intestinal lumen which in turn reduces the absorptive capacity of the small intestine by 50%; then the volume of fluid presented daily to the normal colon would not be the same but, would exceed its maximum daily absorptive capacity and eventually stool excretion of 1000 ml might result, which is termed by definition as diarrhoea. Subsequently, stool volume of greater than 200 ml/24 h would be obtained.

At the cellular level, the main key factor that needs to be considered is the secretion of the chloride ions; whenever there is an efflux of the chloride ions from the cells it results in massive secretion of water into the intestinal lumen leading to watery diarrhoea. The other key events responsible are:

- The activation of adenylyl cyclase
- The inhibition of intestinal Na+, K + - ATPase activity which reduces normal fluid absorption
- Stimulation of prostaglandin formation[6]

Racecadotril

It is a dipeptide which acts peripherally known to having antidiarrheal property. It is basically an Enkephalinase inhibitor which prevents the degradation of Enkephalins. Enkephalins are endogenous opioids found in the body which act on delta opioid receptor and reduces the cyclic AMP level and produces eventually antidiarrheal effect. Therefore, the increased concentration of Enkephalins reduces the hyper secretions of water and electrolyte into the intestinal lumen. Thus, Racecadotril reduces the prevalence of diarrhoea and diarrhoea associated symptoms.[7]

Loperamide

It's an opiate analogue used to control and symptomatic relief of acute nonspecific diarrhoea and of chronic diarrhoea associated with gastroenteritis or inflammatory bowel disease. It acts by slowing intestinal motility and by affecting water and electrolyte movement through the bowel. It inhibits peristaltic activity by a direct effect on the circular and longitudinal muscles of the intestinal wall. Loperamide is a non-selective calcium channel blocker and binds to major peripheral opioid μ(mu)-receptors.[8] It also binds with calmodulin and this direct interaction with calmodulin might be suggested for its antidiarrheal effect. It also has duration of action is longer (12 hr) than diphenoxylate.[9]

Materials and Methods

Drug Procurement

Racecadotril and Loperamide were purchased from local pharmacy. Redotil 100mg (Dr Reddy's Laboratories Ltd) used for Racecadotril and Andial 2mg (Veritaz Healthcare Ltd) was used for Loperamide, although these doses are extremely high for rats based on rat's weight dilutions and calculations were made.

Animals Used

Albino Wistar rats (200-230 g) of either sex were procured from Central Animal House, National College of Pharmacy, Shivamogga, Karnataka. After randomization into various groups all the animals were acclimatized for period of 10 days under standard husbandry conditions: Relative humidity 65±10%; 12 h light/dark cycle. As far as concerned about the diet of the animals, all groups were fed with rodent pellet diet, and water ad-libtium. Ethical clearance (Clearance number: NCP/IAEC/CL/07/2018-19) for performing experiments on animals was obtained from the Institutional animal Ethics committee (IAEC).

Gastrointestinal Motility Test

This test was done as per method of Mascolo et al. and Rahman et al. For this test, selected rats were divided into three groups of five rats in each. At first, 1 mL castor oil was given orally in every rat of each group to produce diarrhoea. After 1 hour, Group I (control group) received saline (2 mL/ kg) orally. Group II received loperamide 5 mg/ kg b.w. orally[10] and Groups III received Racecadotril 10 mg/ kg b.w. orally[11] Group IV received loperamide + racecadotril

in conjugation. After 1 hour, all animals received 1 mL of charcoal meal orally (10% charcoal suspension in 5% gum acacia). One hour after following the charcoal meal administration, all rats were sacrificed and the distance covered by the charcoal meal in the intestine, from the pylorus to the caecum was measured and expressed as percentage of distance moved.[12]

Result

Gastrointestinal Motility Test

The loperamide treated group (Group II) and racecadotril treated group (Group III) showed lessening of gastrointestinal distance (cm to cm) travelled by the charcoal meal in the rats when compared to the control group. Whereas the conjugational dosing regimen of loperamide and racecadotril (Group IV) showed significant lessening of gastrointestinal distance (cm to cm) travelled by the charcoal meal in comparison with their individual doses.

Discussion and Conclusion

Synergism is a remarkable phenomenon of pharmacology, till this date many numerous formulation have been developed and available in the market based on synergistic responses of drugs, also there are products called FDC (fixed dose combinations) which are resultant of synergism. There are several minor ailments like cold, cough, etc. where these FDC products have served as boon to the mankind. Day by day the pharmaceutical companies are developing formulation that have two to three drugs in it for management of diseases, wherein patient doesn't need to take much number of pills instead can consume only a single tablet or capsule. In this study loperamide and racecadotril were given concomitantly which was based on theoretical assumption, yet successfully proved practical implementation also implies the same, the motive for this study was based on the thought and curiosity that till date

Table 1

Group	Treatment	Total length of intestine (cm)	Distance travelled by marker (cm)	Inhibition (%)
Group I	Control	94.33 ± 2.02	81.67± 2.18	---
Group II	Loperamide	96.33 ± 1.45	49.33± 1.20***	39.50%
Group III	Racecadotril	97.00 ± 3.05	62.67± 3.75***	23.45%
Group IV	Loperamide + Racecadotril	99.00 ± 3.51	39.33± 0.88***	51.85%

Note: Data was analysed using one-way ANOVA followed by pairwise comparison. Values are expressed as mean ± S.E.M. n=6, ***P<0.001, **P<0.01and *P<0.05

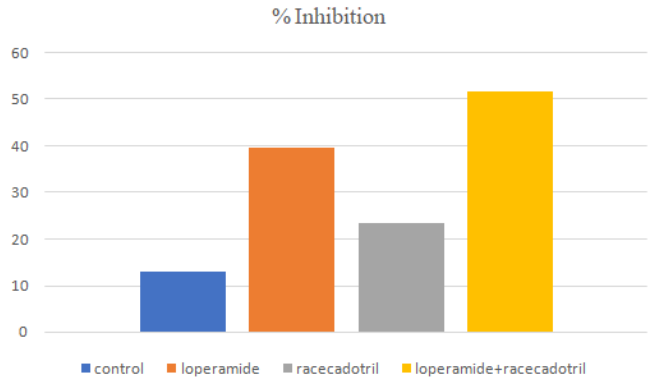

Figure 1.Histogram Showing the Effects of Various groups (Group I - Group IV) on Percentage Inhibition in Gastrointestinal Motility Test

Statistical Analysis

All the values of the data were expressed as mean ± S.E.M. Statistical analysis was carried out by performing one-way ANOVA (one way and multiple way analysis of variance), followed by pair wise comparisons of Tukey's HSD (honestly significant difference) test. A probability level of P<0.05 was considered moderately significant, P<0.01 was considered as significant and P<0.001 was considered as highly significant.

no market available product summons these two drugs, thus this might act as prerequisite for further studies to be conducted and development of a new formulation.

Ethical Approval

Ethical clearance was obtained from the Institutional animal Ethics committee (IAEC), Department of pharmacology, National college of pharmacy shimoga, with Reference number of NCP/IAEC/CL/07/2018-19 to conduct the study in an animal model. The research was performed as per the agreement. Apart from that, all possible steps were taken to avoid animal suffering at each stage of the experiment.

Author Contributions

All the authors have contributed equally to designing, conducting the research, data analysis, drafting or revising the article and have agreed on the journal to which the article will be submitted, gave their final approval of the version to be published, and agree to be accountable for all aspects of the work.

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