COMPARATIVE ACTIVITY TESTING OF LOPERAMIDE HYDROCHLORIDUM WITH OTHER ANTIDIARE DRUG IN WHITE RATS AS AN INTRODUCTION TO DIARY

Lilis Ela Pujiati[1)], Host Bumulo[2)], and Arif Hidayat Arbie[3)]
[1,2,3)] Bina Mandiri University Gorontalo
E-mail: lilisela Pujiati99@gmail.com

ABSTRACT

Diarrhea is still a health problem, especially in developing countries including Indonesia, various kinds of drugs have been used, one of which is Loperamide Hydrochloridum drug with other antidiarrheal drugs. Loperamide Hydrochloridum was chosen because Loperamide Hydrochloridum can inhibit intestinal motility so as to prolong intestinal transit time, reduce the frequency of defecation, increase stool viscosity and prevent electrolyte loss.

This study aims to determine the usefulness or differences of several anti-diarrheal drugs, and to compare the mechanism of action of each anti-diarrheal drug used.

The method used is the experimental method, the experimental method is an experiment to prove a certain question or hypothesis. Experiments can be carried out in a laboratory or outside the laboratory, experimental work implies learning to do, because it can be included in the learning method. The purpose of the experimental method is that students can design, prepare, report, implement, prove and draw conclusions from various facts and information obtained when they conduct their own experiments.

The results showed that in the surgical process of rat 1, the overall length of the intestine was 65 cm and the length of the marker intestine was 30 cm. Rats 2 have a total intestine length of 67 cm with a marker intestine length of 13 cm. For rat 3, the total gut length was 37 cm and the marker gut length was 11 cm. And for 4 mice, the total intestine length was 64 cm with a marker intestine length of 47 cm.

Keywords: *loperamide hydrochloride, diarrhea*

INTRODUCTION

Diarrhea is a disease in which sufferers experience constant stimulation of defecation and the stool or feces has excessive water content. Diarrhea is not a disease that comes by itself. Usually there is a trigger for diarrhea, one of which is due to infection by bacteria or viruses and can also be caused by environmental hygiene factors. A slum and dirty environment becomes a breeding ground for bacteria (E.coli), viruses and parasites (fungi, worms, protozoa), and also flies that play a role in helping the spread of diarrheal disease germs.

The intestine is the main organ for the body's defense. IgA secretory deficiency (sig A) will cause the individual to be unable to cope with bacterial/viral/fungal infections or parasitic infestations in the intestines, as a result germ will multiply freely, with further consequences in the form of chronic diarrhea and more malabsorption of food [1].

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Based on the cause, diarrhea is classified into specific diarrhea and non-specific diarrhea. Specific diarrhea can be caused by pathogenic infections such as viruses, bacteria and parasites. Some of the bacteria that because diarrhea is Staphylococcus aureus, Bacillus cereus, Clostridum perferingrns.

The incidence of diarrhea is quite high according to WHO in 2018, almost two billion people using contaminated drinking water sources are estimated to cause more than 500,000 diarrhea deaths each year and are a major factor in several neglected tropical diseases.

In this practicum, the drugs used are diapet drugs, entrostop and loperamide which can causeantidiarrheal effect. Anti-diarrhea is a drug used to treat diseases caused by bacteria, germs, viruses, worms, or food poisoning. Symptoms of diarrhea are repeated defecation accompanied by a large amount of fluid that comes out sometimes with heartburn and mucus or blood. Diarrhea occurs due to stimulation of the autonomic nerves in the intestinal wall, causing a reflex to accelerate intestinal peristalsis.

Diarrhea is an unusual condition of defecation in which the stools are watery/watery at least three times in 24 hours. Another definition says diarrhea is a clinical symptom of indigestion (intestines) which is characterized by an increase in the frequency of defecation more than usual and repeatedly accompanied by changes in the shape and consistency of the stool to become soft or liquid [2].

The negative consequences of diarrhea are absorption disorders that cause dehydration and malnutrition. Dehydration is a state of lack of fluids, lack of potassium (hypokalemia) and sometimes acidosis (blood becomes acidic), which often ends in shock and death. So that people with diarrhea require replacement therapy with fluids and electrolytes as well as calories, antibacterial or anti-amoebic drugs depending on the cause of diarrhea, as well as other drugs that work to slow intestinal peristalsis, relieve spasm and pain, or soothe [4].

Diarrhea is a disease in which sufferers experience constant stimulation of defecation and the stool or feces has excessive water content. One of the triggers for diarrhea is infection by bacteria or viruses and can also be caused by environmental hygiene factors. A slum and dirty environment is a breeding ground for bacteria (E. coli), viruses and parasites (fungi, worms, protozoa), and also flies that play a role in helping the spread of diarrheal disease germs Diarrhea can cause dehydration (lack of body fluids).

Dehydration can be seen with physical symptoms such as dry lips, wrinkled skin, sunken eyes and crown, and causes shock. To prevent dehydration by drinking ORS solution. Therefore, people with diarrhea should drink lots of water and be given anti-diarrhea medicine. Anti-diarrhea is a drug used to treat diseases caused by bacteria, germs, viruses, worms, or food poisoning. Symptoms of diarrhea are repeated defecation accompanied by a large amount of fluid that comes out sometimes with heartburn and mucus or blood. Diarrhea occurs due to stimulation of the autonomic nerves in the intestinal wall, causing a reflex to accelerate intestinal peristalsis [5].

Determination of the antidiarrheal effect in test animals can be done by observing when diarrhea starts, stool consistency, stool frequency and duration of diarrhea. In vitro in test animals Loperamide inhibits intestinal motility/peristalsis by directly affecting the circular and longitudinal muscles of the intestinal wall and affecting the movement of water and electrolytes in the large intestine.

Antidiarrheals are drugs that when taken when you have diarrhea will show the effect of stopping diarrhea. Substances that suppress peristalsis are actually not very feasible to use because during diarrhea the bowel movement has decreased a lot, besides viruses and toxins need to be removed as quickly as possible from the body. Drugs for the treatment of diarrhea should not be given for more than 7-10 days, because it could be that the diarrhea you are suffering from is not really a diarrheal disease but a diarrheal disease but a symptom of another disease.

Loperamide has an acidity in relation to its chemical formula with the opiate pethidine and has strong anti-inflammatory properties by reducing peristalsis. In contrast to pethidine, loperamide does not act on the CNS (Central Nervous System), so it does not cause dependence. This substance is able to restore cells that are in a state of hypersecretion into normal resorption [17].

Like deifenoxylate, the mechanism of action of loperamide is to inhibit the motility of the digestive tract and affect the circular and longitudinal muscles of the intestine. These drugs are as effective as defonoxylates for the treatment of chronic diarrhea [17].

Loperamide side effects

It does not occur but in children under 2 years it should not be given because there will be strong intestinal peristalsis suppression, causing constipation.

Classification of diarrhea

Classification of diarrhea is divided into 2, namely, based on duration of diarrhea is acute diarrhea is diarrhea that lasts less than 14 days. Acute diarrhea is defined as increased frequency, increased fluid, or increased number of stools excreted, but it is very social to the patient's habits and lasts no more than one week. If diarrhea lasts between one to two weeks, it is said to be prolonged diarrhea [14].

Acute diarrhea can result in loss of water and electrolytes as well as acid-base disorders that cause dehydration, ocial acidosis and hypokalemia, Blood circulation disorders, can be in the form of hypovolemic shock as a result of diarrhea with or without vomiting, Nutritional disorders that occur due to excessive discharge due to diarrhea and vomiting [14].

Chronic diarrhea, namely diarrhea that lasts more than 14 days with weight loss or weight gain during the diarrhea period. Based on pathophysiological mechanisms: 1) Secretory diarrhea viral infections, ocial germs and apatogens such as shigella, ocialc, E. Coli, group vibrio, B. cereus, clostridium perfarings, staphylococcus aureus, small intestine comperastalsis caused by food chemicals (eg food poisoning, spicy food, too sour), psychological disorders (fear, nervousness), nervous disorders, cold, allergies and so on. Osmotic diarrhea This type of diarrhea occurs when too much water enters the stomach. In osmotic diarrhea, the patient's stool will be very watery. One of the causes of osmotic diarrhea is lactose intolerance. This is a condition when the body cannot digest the sugar (lactose) that comes from milk.

How Diarrhea is Transmitted

Diarrhea can be transmitted in various ways that lead to infection, including, Contaminated food and drink, whether contaminated by insects or contaminated by dirty hands:

1. Use of water sources that have been polluted and do not boil water properly.
2. Not washing hands thoroughly after defecating or cleaning infected child's feces, thereby contaminating furniture and tools that are handled [1].

Classification of causes of diarrhea

Classifying the cause of diarrhea in a patient based on the clinical history is

usually difficult. Based on the time of diarrhea can be classified into 3 categories, namely:

1. Acute diarrhea, occurring at least 3 times with liquid stools at an interval of 24 hours.
2. Dysentery, diarrhea with bleeding.
3. Persistent diarrhea, diarrhea for at least 14 days.

Viruses that cause diarrhea

Rotavirus often causes acute diarrhea, especially in infants and children aged 6 to 12 months. Clinical signs include an incubation period of 12 to 48 hours, followed by vomiting, watery diarrhea and low-grade fever [9].

Anti-dairy medication targets

The targets of antidiarrheal therapy include maintaining fluid, electrolyte and acid-base balance, providing therapy for the symptoms, eliminating the cause and treating comorbidities (Dippiro, 1997). The negative consequences of diarrhea are absorption disorders that cause dehydration and malnutrition.

Mechanism of diarrhea

Various microbes such as bacteria, parasites, viruses and molds can cause diarrhea and vomiting. Food poisoning, which causes diarrhea and vomiting, is caused by food and water contaminated by microbes. This paper will explain the mechanism of diarrhea and vomiting caused by microbes through contaminated food. Clinically, the term diarrhea is used to describe an increase in stool liquidity associated with an increase in stool weight or volume and frequency. A person is said to have diarrhea if quantitatively the stool weight per 24 hours is more than 200 grams or more than 200 ml with a frequency of more than three times a day [3].

Diarrhea caused by enteric pathogens occurs by several mechanisms. Some pathogens stimulate secretion of fluids and electrolytes, often involving enterotoxins that decrease salt and water absorption and/or increase secretion of active anions. In this diarrhea condition, there is no osmotic gap and the diarrhea is not related to the contents of the intestine so that it cannot be stopped by fasting. This type of diarrhea is known as secretory diarrhea. Examples of secretory diarrhea are cholera and diarrhea caused by enterotoxigenic E coli [3].

Some pathogens cause diarrhea by increasing the propulsion of muscle contraction, thereby decreasing the contact time between the intestinal absorptive surface and the luminal fluid. This increased propulsion may be directly stimulated by pathophysiological processes activated by pathogens, or by increased luminal pressure due to fluid accumulation. In general, increased propulsion is not considered a major cause of diarrhea but rather an additional factor that sometimes accompanies the pathophysiological consequences of pathogen-induced diarrhea [3].

In some diarrheal infections, the pathogen induces mucosal damage and causes an increase in mucosal permeability. The distribution, characteristics and area of infection will vary between organisms. Mucosal damage that occurs can range from diffusion of pus by the pseudomembrane to fine wounds that can only be detected microscopically. Mucosal damage or increased permeability not only causes the release of fluids such as plasma, but also interferes with the ability of the intestinal mucosa to carry out an efficient absorption process due to back diffusion of the absorbed fluids and electrolytes. This type of diarrhea is known as exudative diarrhea. The cause is pathogenic bacteria that cause invasive infections (Shigella, Salmonella) [3].

Malabsorption of nutritional components in the small intestine often accompanies pathogen-induced mucosal damage. Failure of carbohydrate digestion

and absorption (CHO) will increase with loss of hydrolases on the surface of the microvillus membrane (eg lactase, sucrase-isomaltase) or damage to the microvillus membrane of enterocytes. An increase in solutes in the luminal due to CHO malabsorption causes an increase in luminal osmolality and diffusion of water into the luminal. This type of diarrhea is known as osmotic diarrhea and can be prevented by fasting [3].

Basically, the mechanism of diarrhea caused by enteropathogenic bacteria includes attachment of bacteria to epithelial cells with or without mucosal damage, mucosal invasion, and production of enterotoxins or cytotoxins. One bacterium can use one or more of these mechanisms to overcome intestinal mucosal defenses [3].

Clinical Manifestations

Patients with watery diarrhea pass stools containing large amounts of sodium, chloride, and bicarbonate ions. This loss of water and electrolytes increases with vomiting and water loss also increases with heat. This can lead to dehydration, ocial acidosis, and hypovolemia [10].

Pathophysiology

There are four pathophysiological mechanisms of electrolyte disturbances in diarrhea. The four mechanisms that form the basis of diagnosis and therapy include changes in ion transport activity by decreased sodium absorption or increased chloride secretion, changes in intestinal motility, changes in intestinal osmolarity, and increases in smooth muscle hydrostatic pressure. In the clinic, this mechanism can be related to the types of diarrhea, namely secretory, osmotic, exudative, and changes in intestinal transit.

Dehydration is the most dangerous condition because it can cause hypovolemia, cardiovascular collapse and death if not treated properly. Dehydration that occurs according to plasma tonicity can be in the form of ocial dehydration, hypertonic (hypernatremic) dehydration or hypotonic dehydration. According to the degree of dehydration oci without dehydration, mild dehydration, moderate dehydration or severe dehydration

Diarrhea Treatment

Treatment of diarrhea can be done by means of chemotherapy. For causal therapy that destroys disease-causing bacteria, sulfonamides or antibiotics are used:

1. Obstipansia, namely for symptomatic therapy with the aim of stopping diarrhea, namely by:
   a. Suppress intestinal peristalsis (loperamide)
   b. Shrink the intestinal lining or astringents (tannins)
   c. Administration of adsorbents to absorb toxins produced by bacteria or other diarrhea-causing toxins (carbo adsorbents, kaolin).
2. Giving mucilage to protect the mucous membrane of the injured intestine.
3. Spasmolytic, which is a substance that can relax stomach muscle spasms (abdominal pain) in diarrhea (ocialc sulfate).
4. Probiotics to increase endurance Lactobacillus and bifidobacteria (Lactid Acid Bacteria/LAB) are probiotics that can produce natural antibiotics that can prevent/inhibit the growth of pathogenic bacteria. LAB can produce lactic acid which causes the pH of the intestine to become acidic, the acidic environment will inhibit the growth of pathogenic bacteria. This LAB can help strengthen and improve baby's digestion, preventing diarrhea [1].

Description of Experimental Animals

Classification of Experimental Animals

White rat (Rattus norvegicus)

Kingdom : Animalia

phylum : Cjordata

Class : Mammals
Order : Rodentia
Sub Order : Odontoceti
Family : Muridae
Genus : Rattus
Species : *Rattus Norvegicus*

Animal morphology and anatomy

White rat (Rattus norvegicus), house rats are 65-95 mm long from the tip of their nose to the tip of their body. Their fur ranges in color from light brown to black and is generally white in color. Rats have long tails that have little fur and have a ring of scales. tend to have a darker tail feather length when living closely with humans, humans range from 12-30 grams in body weight. Many domestic forms of mice have been developed that vary in color from white to black and with spots [15].

Test Animal Characteristics

White rat (Rattus norvegicus)
Lifespan: 2-3 years can be up to 4 years
Long pregnant: 20-22 days
Mating after giving birth: 1 to 24 hours
Age weaned: 21 days
Mature age: 40-60 days
Mating age: 10 weeks (male and female)
Etrus cycle: 4-5 days
Long Etrus: 9-20 hours
Mating: at the time of Etrus
Ovulation: 8-11 hours
Number of children: average 9-20
Group marriage: 3 females with 1 male [5].

Material Description

Loperamide (ISO, 2014)
Official name: Loperamidi Hydrochlorid-um
Other Names: Loperamide Hydrochloride, Loperamide HCl
RM/BM: C29H33CIN2O2.HCl/513.51
Description: White to slightly yellow powder, melts at a temperature of about 225o with decomposition.
Solubility: Easily soluble in methanol, in Isopropyl alcohol and in chloroform, sparingly soluble in water and in dilute acids.
Indication: Loperamide-HCl is used to treat non-specific acute diarrhea and chronic diarrhea caused by inflammation of the digestive tract.
half-life: 7-14 hours
Dosage: Initial dose of 4 mg, then every hour 2 mg a maximum of 16 mg daily.
Uses: Diarrhea medicine

RESEARCH METHODS

Experimental method

Tools and materials

The tools used in this experiment were surgical instruments, oral probes, rulers, wooden mats. While the materials used are experimental animals Loperamide Hcl, entrostop, diapet, Chinese ink.

Work procedures

Prepare tools and materials and provide experimental animals, the rats are marked so as not to be confused during observation, then the rats are weighed, then the rats are treated, after that prepare the dispo and cannula which already contains 1 ml of diapet solution, insert the cannula into the rat's mouth after that left for 30 minutes. The second, third and fourth mice were given the same treatment as the first experiment. The second rat was given the drug entrostoptikus, the third was given Nacl and the fourth rat was given loperamide, then the rat was left for 30 minutes and then given Chinese ink orally.

RESULTS AND DISCUSSION

Research result

From the results of the study, the experimental animals were divided into four groups, namely rats one, rats two, rats three and rats four. For the first rat, the body weight was 55.83g and the total intestine length was 65 cm, the marker intestine length was 30 cm. for two rats, the animal weight is 65.56g, the total

intestine length is 67 cm, the marker intestine length is 13 cm. the third rat with a body weight of 67.86 g with a total intestine length of 37 cm and Markwer's intestine 11 cm long. The last one is rat four has a body weight of 60.36 g with a total intestinal length of 64 cm and a marker intestine length of 47 cm.

Discussion

Aims to determine the usefulness or differences of several anti-diarrhea drugs, and to compare the mechanism of action of each anti-diarrheal drug used. Diarrhea basically does not need medication, only if there is severe diarrhea, drugs can be used to reduce it. Antidiarrheal drugs that are widely used include diapet whose work power can normalize the resorption-secretion balance of mucosal cells, which is to restore cells that are in the body. hypersecretory state in a state of normal resorption again. Diapet with 2–3 stronger obstipating properties without CNS efficacy, so it does not cause dependence.

In this experiment, a diarrhea drug test was conducted. This experiment aims to make the practitioner know how far the drug works. The experimental animal used in this experiment was a white rat (Rattus norvegicus). Apart from having the same physiological anatomy as human anatomy, also because mice are easy to handle, their body size is small so that research time can take place more quickly. Before being used for the experiment, the rats were fasted for 18 hours before the experiment. This is because the food in the intestine will affect the speed of peristalsis. This experiment was carried out by giving orally, i.e. the drug is injected by mouth. With oral administration, it is because it is simple and easy to do. The test animals were observed whether there was an effect or not.

This time the practicum was carried out by providing experimental rats, tools and materials. The first procedure was Rats were marked so as not to be confused during observations. Then the rats were weighed to calculate the dose of the drug to be given. The dose of the drug is directly proportional to the rat's body weight so that if there is a difference in body weight, the dose given must be different in order to give the appropriate effect. The rats used must be rats that were being fasted before because if they were not fasted, the possibility of inaccurate observations was greater because of the presence of food that still digested in the stomach or intestines of rats which can affect the passage of the marker substances used due to the digestion of food. The marker substances used are markers.

The experiment this time was carried out, namely Giving treatment to the experimental animals was first carried out by first holding the correct rat, namely by lifting the tail end of the rat with the right hand and removing it from the cage and then placing it in a place with a rough surface (for example, on a wire frame on the cage cover and a rough cloth), then taming it with how to stroke the bend of the mouse using the index finger. Stress in rats is indicated by red eyes of rats and rats become wild. Then after the rat is calm we pull the skin on the nape of the rat with the index finger and thumb of the left hand, and the right hand holds the tail and then turns the rat's body so that it faces up and pinches the tail with the little finger and ring finger of the left hand. After giving treatment to the experimental rats (Rattus novergicus), Diapet serves as an adstringensia that will shrink the intestines so that feces do not come out easily and reduce the frequency of defecation. Then insert the cannula into the rat's mouth. After inserting the diapet solution into the rat's mouth. After that, the rat is left for 30 minutes.

The second, third and fourth experimental animals were given the same treatment with different drugs. For rats 2

were given the drug entrostop. Entrostop, which can relieve symptoms of abdominal pain, rat three was given NaCl solution and rats four were given loperamide. Loperamide, which is used to treat diarrhea. Each solution was put into a dispo of 1 ml. Then the rats were left for 30 minutes, the rats were then given Chinese ink orally. The time given for 30 minutes was intended so that the pharmacological effects of the drug could be achieved when the marker was given, because drugs given orally usually had a longer effect than drugs given parenterally.

Chinese ink is very thick in color so it is suitable for use in this observation which will give black marks on the intestines of mice. Prior to animal surgery, the mice were anesthetized using chloroform. In the process of dissecting rat 1, the total intestine length was 65 cm and the marker intestine length was 30 cm. Rats 2 have a total intestine length of 67 cm with a marker intestine length of 13 cm. For rat 3, the total gut length was 37 cm and the marker gut length was 11 cm. And for 4 mice, the total intestine length was 64 cm with a marker intestine length of 47 cm. The total length of the intestine is 37 cm and the marker intestine is 11 cm. And for 4 mice, the total intestine length was 64 cm with a marker intestine length of 47 cm. The total length of the intestine is 37 cm and the marker intestine is 11 cm. And for 4 mice, the total intestine length was 64 cm with a marker intestine length of 47 cm.

CONCLUSION

Diarrhea is a disease in which the sufferer experiences constant stimulation of bowel movements and the stool or feces has an excessive water content. Antidiarrheal drug activity can inhibit diarrhea. One way to prevent diarrhea is by suppressing intestinal peristalsis. The intestinal transit method can be used to determine the percentage of peristaltic inhibition of an antidiarrheal drug. Anti-diarrhea is a drug used to treat diseases caused by bacteria, germs, viruses, worms, or food poisoning. Symptoms of diarrhea are repeated defecation accompanied by a large amount of fluid that comes out sometimes with heartburn and mucus or blood. Diarrhea occurs due to stimulation of the autonomic nerves in the intestinal wall, causing a reflex to accelerate intestinal peristalsis.

In the process of dissecting rat 1, the total intestine length was 65 cm and the marker intestine length was 30 cm. Rats 2 have a total intestine length of 67 cm with a marker intestine length of 13 cm. For rat 3, the total gut length was 37 cm and the marker gut length was 11 cm. And for 4 mice, the total intestine length was 64 cm with a marker intestine length of 47 cm.

Suggestion

Practitioners are expected to pay more attention during the practicum and must be more careful in handling test animals so that the test animals do not injure the practitioner.

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