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Effect Test Of Analgetics (Paracetamol, Ibuprofen and Antalgin) in Local Strain Male Mice With Acetic Acid Induction Using The Writhing Test Method

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ABSTRACT
Analgesic or pain blocking drugs are compounds that reduce / eliminate pain without causing loss of consciousness. NSAID (non-steroidal anti-inflamatory drugs) or non-steroidal anti inflammatory drugs, are heterogeneous compounds due to the different chemical structures of NSAID compounds, which are used to reduce mild to moderate pain, such as paracetamol, mefenamic acid and ibuprofen. Paracetamol is used to reduce body heat caused by infection or something else. In addition this drug also relieves pain at a mild to moderate level, this analgesic works directly on the bodys heat regulating center in the hypothalamus. **The method** use is writing test with acetic acid induction. **The result** of this study indicate that testing the effectiveness of the paracetamol, ibuprofen and antalgin analgesic drugs in mice did't yield greater writhing than control mice.
Keyword : analgesic, mice, writhing test, acetic acid

I. Introduction

Analgesic drugs are drugs that can reduce or eliminate pain and will ultimately provide a sense of comfort to people who are suffering. Pain is a uncomfortable sensory and emotional feeling associated with the threat of tissue damage. Pain in most cases is only a symptom that serves as a warning signal about a disorder in the tissues such as inflammation, rheumatism, gout or muscle spasms.Pain receptors (nociceptors) are free nerve endings, which are scattered in the skin, muscles, bones and joints. Pain impulses are channeled to the central nervous system through two pathways, namely the fast pain pathway with the neurotransmitter glutamate and the slow pain pathway with the neurotransmitter substance (Benni Iskandar1, 2021).

All pain compounds (pain mediators) such as histamine, bradykin, leukotrienes and prostaglandins stimulate pain receptors (nociceptors) on free nerve endings in the skin, mucosa and other tissues and thus cause inflammatory reactions and convulsions. This nociceptor is also present in all tissues and organs of the body, except in the CNS. From here, stimuli are channeled to the brain through a dense network of neurons with numerous synapses via the spinal cord, spinal cord and midbrain. From the thalamus the impulse is then forwarded to the pain center in the cerebrum, where the impulse is felt as pain. Pain is in most cases only a symptom that serves to protect the body. Pain should be considered as a danger signal about a disturbance in the tissue, such as inflammation, infection of microorganisms, or muscle spasms. Pain caused by mechanical, chemical or physical stimulation can cause tissue damage. This stimulation triggers the release of certain substances called pain mediators. Pain mediators, among others, can cause inflammatory reactions and convulsions that activate pain receptors on free nerve endings in the skin, mucosa and other tissues. These nocireceptors are present in all tissues and organs of the body, except in the CNS. From here stimulation is channeled to the brain through a dense network of neuronal levels with numerous synapses via the spinal cord, spinal cord, and midbrain. From the thalamus the impulse is then forwarded to the pain center in the cerebrum, where the impulse is felt as pain. (Lessells et al., 2011).
a. Nonopioid/Peripheral Analgesics(Non-Opioid Analgesics)

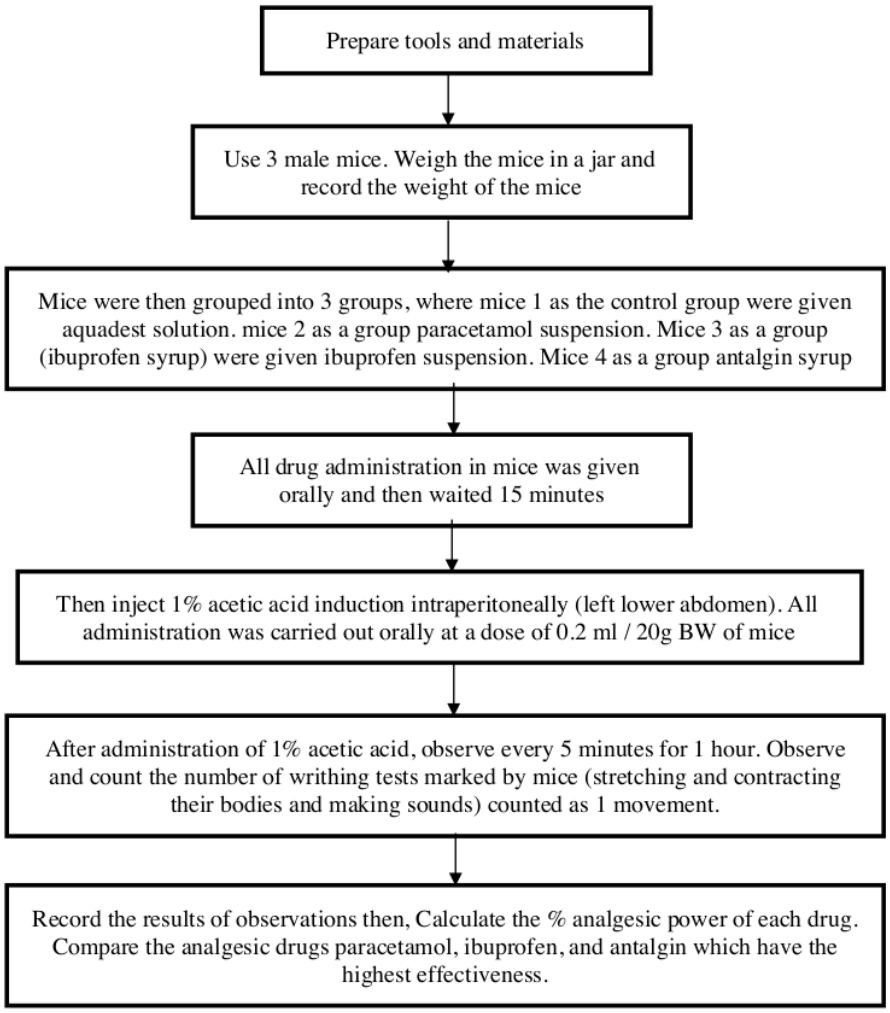
Practically pharmacologically, it is divided into salicylates (acetosal, diflunisal) and nonsalicylate groups. Most of the non-salicylate preparations include as.Arylalkanoic derivatives (Gilang, 2010).

b. Opioid Analgesics/Narcotic Analgesics

Its main mechanism of action is to inhibit the cyclooxygenase enzyme in the formation of prostaglandins which is associated with its analgesic action and side effects. Most NSAID analgesics are thought to act peripherally. Its analgesic effect has been seen within one hour after oral administration. While the anti-inflammatory effects of NSAIDs have been seen within one-two weeks of administration, the maximum effect appears to vary from 1-4 weeks. After oral administration, peak blood levels of NSAIDs are reached 1-3 hours after administration; absorption is generally not affected by the presence of food. It has a relatively small volume of distribution (<0.2 L/kg) and is usually highly bound to plasma proteins (>95%). The elimination half-life for arylalkanot derivatives is around 2-7 hours, while the half-life of indomethacin varies greatly between individuals who use it, while piroxicam has the longest half-life (45 hours) (Gilang, 2010).

II. The Proposed Method/Algorithm Reasearch

The method used is the writhing test by induction using acetic acid and then calculating the stretching of each mouse that has been given analgesics compared to the control. the research was conducted at the pharmacology and toxicology laboratory of IIK Strada Indonesia in August-November 2022. Algorithm Reasearch in this study :



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III. Method

A. Preparation of research materials by making paracetamol suspension dose calculation.

a. The usual dose of Paracetamol for humans = 500 mg

Dosage conversion for mice with BB 20 g = Usual Dose x Conversion Factor = 500 mg x 0.0026 = 1.3 mg. For mice weighing 35.17 g = (35.17 g/ 20 g) x 1.3 mg = 2.28 mg. This dose is given in volume = 0.2 ml. A supply solution of = 100 ml is made Amount of paracetamol used = (100 ml / 0.2 ml) x 2.28 mg = 1140 mg or 1.140 g % paracetamol level = (1.140 g / 100ml) x 100% = 1.14 %. Preparation of Na solution. CMC 1%. Take 1 gram of Na.CMC, put it in a mortar and add 25 ml of warm water (60°C) for 30 minutes, then stir until homogeneous in a beaker, then add volume up to 100 ml.

b. Paracetamol tablets are used

Taking paracetamol tablets = 510 mg tab weight powder taken = 1140 mg/1500 mg x 1530 mg = 1162.8 mg made suspension. Take 3 pct tablets and grind them until smooth. Enter the PCT powder that has been weighed into the mortar, add about 50 ml of CMC sodium solution, stir until homogeneous. Transfer the PCT suspension into a beaker glass then make up the volume to 100 ml with distilled water

c. Calculation of oral acetaminophenum dose for mice 3

The usual dose of Paracetamol for humans = 500 mg. Dosage conversion for mice with BB 20 g = Usual Dose x Conversion Factor = 500 mg x 0.0026 = 1.3 mg. For mice weighing 21.20 g = (21.20 g/ 20 g) x 1.3 mg = 1.378 mg. This dose is given in volume = 0.2 ml. A supply solution of = 100 ml is made. Amount of paracetamol used = (100 ml / 0.2 ml) x 1.378 mg = 689 mg or 0.689 g. % paracetamol level = (0.689 g / 100ml) x 100% = 0.689 %.

B. Preparation of research materials by making ibuprofen suspension dose calculation.

a. Preparation of Ibuprofen Suspension

Calculation of oral doses of Ibuprofen for mice 2. The usual dose of Ibuprofen for humans = 400 mg. Dosage conversion for mice with a weight of 20 g = Usual Dose x Conversion Factor = 400 mg x 0.0026 = 1.04 mg. For mice weighing 24.38 g = (24.38 g/ 20 g) x 1.04 mg = 1.27 mg. This dose is given in volume = 0.2 ml. A supply solution of = 100 ml is made. The amount of ibuprofen used = (100 ml / 0.2 ml) x 1.27 mg = 635 mg or 0.635 g. % levels of ibuprofen = (0.635 g / 100ml) x 100% = 0.635 %

b. Ibuprofen syrup is used. If in the experiment using ibuprofen syrup, it is known that the ibuprofen syrup contains 100 mg ibuprofen per teaspoon (5 ml). Ibuprofen syrup concentration = 100 mg / 5 ml. The amount of ibuprofen needed = 635 mg. So the amount of ibuprofen syrup taken = (635 mg/ 100 mg) x 5 ml = 31.75 ml

c. Calculation of oral doses of Ibuprofen for mice 3

The usual dose of Ibuprofen for humans = 400 mg. Dosage conversion for mice with BB 20 g = Usual Dose x Conversion Factor = 400 mg x 0.0026 = 1.04 mg. For mice weighing 23.30 g = (23.30 g/ 20 g) x 1.04 mg = 1.2116 mg. This dose is given in volume = 0.2 ml. A stock solution of = 100 ml is made. The amount of ibuprofen used = (100 ml / 0.2 ml) x 1.2116 mg = 605.8 mg or 0.605 g. % levels of ibuprofen = (0.609 g / 100ml) x 100% = 0.605 %

C. Preparation of research materials by making ibuprofen suspension dose calculation.

a. Calculation of Antalgin oral dose for mice 2

The usual dose of Antalgin for humans = 500 mg. Dosage conversion for mice with BB 20 g = Usual Dose x Conversion Factor = 500 mg x 0.0026 = 1.3 mg. For mice weighing 38.68 g = (38.68 g/ 20 g) x 1.3 mg = 2.5142 mg. This dose is given in volume = 0.2 ml. A supply solution of = 100 ml is made. Amount of antalgin used = (100 ml / 0.2 ml) x 2.5142 mg = 1257 mg or 1.257 g. % antalgin content = (1.257 g / 100ml) x 100% = 1.257 %

b. Antalgin syrup is used

If the experiment uses Antalgin syrup, it is known that Antalgin Syrup contains 250 mg of Antalgin per teaspoon (5 ml), because this experiment requires 1257 mg of Antalgin.

So to make antalgin suspension 1.257%. Antalgin syrup concentration = 500 mg / 5 ml

The amount of Antalgin needed = 1257 mg. So the amount of Antalgin syrup taken = (1257 mg/ 500 mg) x 5 ml = 25.14 ml

D. Analisys

$$\% \text{ Analgetic Power} = \frac{Number\ of\ stretches\ in\ the\ treatment}{number\ of\ stretches\ in\ the\ control}\ x\ 100\%$$

IV. Results and Discussion

Analgesics are drugs or compounds used to reduce or dispel pain or tenderness. The purpose of this study was to compare the analgesic power of paracetamol and acetosal drugs using chemical stimulation methods. This experiment was carried out on experimental animals, namely rats. The chemical stimulation method is used based on the pain stimuli elicited by chemical substances used for the determination of analgesic power.

In this study the analgesics used were paracetamol, ibuprofen and antalgin. By using aquadest control. This practicum uses the stretching method or the Witkin method due to chemical induction. The pain that arises will be known by the reaction carried out by the mouse, namely by stretching in the form of pulling the legs back, pulling back the abdomen (reaction) and tetanic spasms by bending the head and legs backwards.

Administration of test materials in this study used two ways, namely intraperitoneal and orally. To find out the action of analgesics on mice, it is necessary to condition them by making them feel pain using acetic acid. The use of acetic acid as an inductor of pain because acetic acid is a weak acid that is not conjugated in the body, administering acetic preparations to experimental animals will stimulate prostaglandins, to cause pain due to tissue damage or inflammation.

Prostaglandins cause sensitization of pain receptors to mechanical and chemical stimulation so that prostaglandins can cause a state of hyperalgesia, then chemical mediators such as bradykinin and histamine stimulate them and cause real pain, so that the mice will stretch their legs backwards when the effect of this inducer works. Acetic acid is given by intraperitoneal (i.p) administration route which is injected into the abdominal cavity in the middle of the stomach line slightly sideways with an injection syringe measuring 1 ml/cc.

Based on the results of this study, the following data were obtained :

Table 1. Amount Writhing of Mice

Minute	Amount Of writhing			
	Mice 1 (control)	Mice 2	Mice 3	Mice 4
0-5	5	5	9	-
6-10	13	15	10	-
11-15	17	20	12	-
16-20	13	12	12	2
21-25	23	20	14	1
26-30	10	18	20	3
31-35	8	10	14	2
36-40	4	10	13	1
41-45	3	7	16	1
46-50	3	11	10	2
51-55	3	2	6	1
56-60	-	3	2	1
Cumulative Amount	92	133	136	14

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The results of this study showed that mice 1 (control) showed 92 writhing where as the control was injected with aquadest, while the second mice injected with paracetamol showed 133 writhing results, the third mice were injected with ibuprofen syrup showed 136 writhing results and the fourth mice were injected with antalgin syrup shows as many as 14 wriggles.

a. % Analgetic Power mice 2 $= \frac{133}{92} x\ 100\% = 144{,}6\ \%$
b. % Analgetic Power mice 3 $= \frac{136}{92} x\ 100\% = 147{,}8\ \%$
c. % Analgetic Power mice 3 $= \frac{14}{92} x\ 100\% = 15{,}2\ \%$

From the experimental results, it was found that the amount of writhing in mice given the analgesic antalgin was much less than the amount of writhing in mice given paracetamol. This is inconsistent with the statement which states that Paracetamol has a central analgesic effect and inhibition of prostaglandin production through inhibition of COX-2 activity which is equivalent to NSAIDs. Paracetamol's ability to inhibit cyclooxygenase-1 (COX-1) enzymes is lower than NSAIDs (Arslan et al., 2013). Cyclooxygenase-1 functions in normal physiological regulation to protect gastrointestinal, renal, and platelet function. Lower COX1 enzyme inhibition compared to NSAIDs makes paracetamol safer. There are differences in the activity of all drugs that are antipyretic, analgesic, anti-inflammatory. As an analgesic and antipyretic, paracetamol is only effective for pain with low to moderate intensity. However, it has high effectiveness against antipyretics. This is because analgesics inhibit Cox-2, whereas as antipyretics inhibit Cox-3 which is directly on the central nervous system in the hypothalamus or brain barrier (Katzung, 2011).
Antalgin is one of the NSID groups that works by inhibiting the cyclooxygenase (COX) enzymes, namely COX-1 and COX-2. The COX-1 enzyme acts as a prostaglandin catalyst to protect the gastric mucosa. Inhibition of COX-1 by NSAIDs induces gastric damage. COX-2 works by stimulating an inflammatory response and catalyzing prostaglandins to produce an inflammatory response (Lelo, 2001). The anti-inflammatory effect of antalgin comes from COX-2 inhibition.

V. Conclusion

The conclusion in this study is that each analgesic has different effectiveness so that the results obtained from this study indicate different tickling in mice. from this study showed that the analgesic power of antalgin was the best compared to paracetamol and ibuprofen..

Acknowledgment *(HEADING 5)*

More in-depth research is needed so that the results are more accurate and precise.

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