

EVALUATION OF VARIOUS TECHNIQUES TO DETERMINE IN ANALGESIC ACTIVITY

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ABSTRACT

These reviews try to create easy to get to an indication of reported analgesic activities of plants with models of in-vivo. The World Health Organization (WHO) pain ranking their response to other treatment determines the optimal of the agent. Pain is stimulated by pain receptors and their stimulus is moving on by specific nerve's spinal cord and from there brain from including to North America as acetaminophen or basically APAP (paracetamol), the non-steroidal anti-inflammatory drugs (NSAIDs) such as the salicylates or opioid drugs such as morphine and oxycodone. When did choosing analgesics, the severity? Types of Analgesic- Local anesthetics,

NSAIDs, paracetamol, or Opioids. The insight of pain is due to the beginning of the nociceptive receptor by the neurotransmitters. In receptors have been identified for the pain perception, there are 3 type's mu (μ), kappa (κ) and delta (δ).

KEYWORDS: Analgesia, Analgesic Models, Action of Analgesic Drugs, Mechanism.

INTRODUCTION

Pain is a difficult sensation frequently produced by extreme or harmful stimuli. The International Association for the Study of Pain's broadly used explanation defines pain as "a disagreeable bodily and responsive experience connected with real or potential tissue damage,^[1] or labeled in terms of such damage" Pain stimulates pain receptors, and this stimulus is transmitted via studied nerves to the spinal cord and from there to the brain. Pain receptors are current universally in the body, specifically the skin, surfaces of the joints,

Periosteum (the particular inside layer around the bone), walls of the blood vessel, and definite structures in the skull. Other organs, such as the gut and muscles, have more pain receptors. Pain receptors are free nerve endings.

There are three types of pain receptor stimuli

- a) **Mechanical:** a mechanical stimulus would be, for example, high pressure or stretching.
- b) **Thermal:** a thermal pain stimulus would be dangerous heat or cold.
- c) **Chemical:** In the outside world (e.g. acids) pain receptors are stimulated by chemicals because assured products were existing in the body and released as a result of trauma, inflammation or other painful stimuli. These elements for some Examples are potassium ions, bradykinins, serotonin and acids (such as lactic acid, which muscle pain after heavy exercise).

An analgesic or painkiller is any member of the group of drugs used to achieve analgesia, relief from pain. In the various effective ways on the peripheral and central nervous systems Analgesic drugs act. For the include paracetamol (known in North America as acetaminophen or simply APAP), Analgesics. As the non-steroidal anti-inflammatory drugs (NSAIDs) such as the salicylates, and opioid, morphine and oxycodone drugs. When choosing analgesics, the severity and response to other medication determine the choice of agent; the World Health Organization (WHO) pain ladder.^[2]

Types of Analgesic agents

(A.) Local anesthetics

Provide analgesia by acting directly at nerves near the required site and inhibiting transmission of Painful stimuli back to the brain. It may be injected into tissues and allowed to perfuse around nerves, or applied topically to skin and given time to permeate through. The time required for lignocaine based preparations to be effective at numbing skin will vary according to the drug preparation, species, and their skin type. Compared to lignocaine, bupivacaine has a significantly slower onset of action, a prolonged duration of action and cannot be safely given intravenously. There may be transient pain associated with injection of local anesthetic agents; for this reason, they should preferably be used in anesthetized animals. The use of these agents in the conscious animal should be considered in the context of the species and the procedure, with the method that causes the least distress or discomfort selected.

e.g. - Lignocaine, Bupivacaine.

(B.) Non-Steroidal Anti-Inflammatory Drugs- NSAIDs

This class of drugs act as non-selective inhibitors of cyclooxygenase (COX) enzyme and are known to have analgesic and anti-inflammatory effects.

e.g. - Meloxicam, carprofen.

(C.) Paracetamol

Generally classed on its own, this is a COX-2 selective drug that can be safely combined with NSAIDs or opioids for multi-modal analgesia. Paracetamol has a narrow safety margin in many animals and is lethal if given to cats.

(D.) Opioids

Act at opioid receptors (primarily μ or κ) to provide analgesia, though common side effects may also include sedation, respiratory depression, euphoria or constipation. As each species group has varying types and ratios of these receptors, the effects of the agent may vary in different species.

Investigators need to be aware of any species differences before selecting opiates for procedures and should consult with the AWO or a veterinarian where required. It should be noted that for some reptile groups, the use of certain opioids has been shown to be ineffective for analgesia.

e.g. - buprenorphine, butorphanol.

Mechanism of Analgesic Drugs

The perception of pain is due to activation of the nociceptive receptor by the neurotransmitters. Three receptors have been identified for the pain perception, mu, kappa, and delta. Prostaglandin I or prostaglandin II or sometimes both of starting in initiate the synthesis. The analgesic drugs block them for selectively or none selectively to the COX-II receptor. The opioids' relieve to pain increasing at the spinal cord level, it may be the bigger level of pain with individual and withstand.^[3,4]

Models for Analgesic Activity**A. Thermal stimulus****a.) Hot Plate Method**

This method of analgesic evaluation is established on the thermal stimuli principle. The animal used in this procedure firstly presented to the pain by put on heat to their paw.^[5,6,7]

This will root pain and after few minute rats will start, licking their paw and trying to standpoint by one leg for the moment and then inject the medicine or plant extract, which is to be evaluated. The hot plate temperature must be maintained at 55°C consistently.^[8-9]

Methodically procedure is as follows

- The mice/rat used for the experiment on Evaluate and number.
- Dived animals into three groups- (1) Reference (2) Control (3) Experimental Groups.
- I note down the time of reaction for the rat by licking or jump response in the animal after placing them on the hot plate a cut off time will be about 15 sec to escape superfluous pain and damage.
- Insert the drug (Plant extract) on experimental animal and allow the drug to be absorbed, and again place them on the hot plate and note down the basal reaction time.
- Before and after Insert medicine compare the response time.
- Repeat procedure if suitable result or response is not received.

b.) Tail Flick Method: There are second most broadly used animal study model for evaluating the activity of analgesic in either mice or rat.^[10]

Procedure

- Procedure on the simple principle as the tail of mice comes with contact to heat or thermal stimuli it determination try to remove his tail or flick his tail from the stimuli source.
- It appearances the regular reaction time for the pain observation and careful as the final point.
- This behavior is also appropriate for human.^[11-12]
- After the tail flicking by a rat, they are treated with given analgesic treatment and then again, their response time is noted.

If that drug has analgesic, property there will be the delay in response time.^[13] Normally, rat show response in 3 to 5 seconds, if it takes extra in 10-12 second than those rats will remove from trials to avoid additional damage.^[14-15]

B. Electric stimulus

a.) Electrical Stimulation in Tail.

Procedure

- Electrical stimulation on tail also gives suitable result in the evaluation of analgesic drugs.

- When an electrode is injected intravenously in the tail of the rat and linked to the electric source which supplies a very insignificant current of about 40-50 V.
- When current is supplied rat pledge the reflex action, this reflex beginning time is recorded and calculated for the analgesic effectiveness when the analgesic drug is injected in the rat. This process has one disadvantage that animal may feel more pain than usual and sometimes death may be possible.^[16-17]

b.) Grid Shock Test: In this model, mice are used for the evaluation purpose. They were placed in the chamber before the experiment so that they may become familiar to the assembly.^[18] This assembly is made of a plastic chamber, which is equipped with the wired mesh at the bottom. The stimulus was given in the form of electrical photons, on 30-32 cycles per second bases for a maximum of 02 minutes to avoid any injury.^[19] After initiation of current flow, mice try to escape or jump from that surface. Then this activity may be recorded either by using an oscilloscope or by simply slow motion video recorder. The same activity is repeated after the injection of the drug at every 15-minute interval.^[20]

Procedure

- Weigh and number the mice/rat used for an experiment.
 - The animals were divided into three groups- (1) Reference (2) Control (3) Experimental Groups.
 - The reaction time was Note down of rat by put on current at the grid.
- The drug (Plant extract) was injected into the experimental animal and allow the drug to be absorbed, and again place them to thermal stimulus source and note down the basal reaction time.
- Before and after Insert medicine compare the response time.

c.) Tooth Pulp Stimulation: Tooth pulp stimulation as the name indicates involve the removal of tooth pulp from an experimental animal, in this case, the rabbit is used as in vivo animal.

Procedure

- Firstly, a rabbit of around 3 kg has been anesthetized with 15 mg/kg fentanyl-citrate intravenously than pulp chamber will be removed up to visualization of the gingival line so that the root sensitivity may achieve.

- This whole process is done by a sterilized driller and electrode is inserted into that cavity and a small frequency of the current is applied with 0.2 mA and slowly increase if the licking does not appear.
- Sometimes the current velocity is gradually increased and then decreased to active the exact threshold of the current.
- To get the accurate result this procedure is repeated 3-4 times and finally, the drug to be evaluated is injected intravenously to see the potency and efficacy.^[21-22]

C. Chemical stimulus

a.) Acetic Acid Writhing Test: Painful stimulation can also produce by chemical substance as the evolutionary method^[23] for this purpose generally acetic acid, phenyl Quinone, bradykinin is used by injecting them into the peritoneal cavity of rat/mice - When chemicals injected into them, they start writhing due to pain. Pain is also complied with abdominal cramp, discomfort, twisting of hind legs and extension of the body. These symptoms are used as a signal of pain. If given analgesic drug reduces these symptoms of pain, this will be considered effective. Narcotic and non-narcotic analgesic is used for the relieving of pain caused by the writhing.^[24-25]

Procedure

- Weigh and number the mice/rat used for the experiment.
- Dived animals into three groups- (1) Reference (2) Control (3) Experimental Groups.
- Administer the appropriate volume of acetic acid solution to the experimental group.
- Note the onset of writhing. Record the number of abdominal contraction, turn and twist response and extension of a limb for the duration of 10 minutes.
- Inject the drug (Plant extract) on experimental animal and allow the drug to be absorbed, and again repeat the procedure by injecting acetic acid
- Before and after Insert medicine compare the response time.

Ant nociceptive activity can also be expressed by percent maximal possible effect (%MPE)
% MPE= Mean within the treated group - Mean control with/ cut off time (Sec) - mean control with $\times 100$.

b.) Formalin-Induced Writhing: Formalin-induced writhing in the rat is measured for the evaluation for the chronic pain when considered is model of rat. The anti-inflammatory drug is used to always of formalin and it evaluates here in the test of the International Journal of Neurologic Physical Therapy 2016; 2(6): 44-50 48.

Procedure

- In the 37% solution of formaldehyde is injected by the front paw of the rat for the analgesic drug.
- Few minutes after the injection its paw becomes swollen and pain starts.
- After starting of the pain, the rat lacking and biting of own paw so this indication well is recorded.

Like a walk of the rat with its full paw or jumping behavior to protect its own paw, it could be a different parameter is noted.^[26-27] After injection of the analgesic drug, this indication is also completely repeated.

Other Various Models for Analgesic Activity

A.) Mechanical stimulus

a.) Haffner's Tail Clip Methods

Haffner gave to this technique of determining analgesic are around in 1929.

Procedure

- This technique according to if the tail is clipped with any object and tightly or will be compression generation of pain in tail as well as mice starting to bite that portion of its tail.
- By using this simple yet important marvel, we may apply the drug to be evaluated and record the response whether it bites tail quickly or in potential.^[28-29]
- If given drugs have analgesic likely than rat will not bite its tail so frequently.
- Mice that do not show any response within 15 seconds will reject from the experiment.^[30]

b.) Tail Immersion Method

Analgesic activity was also tested in Wistar albino rats by the caudal immersion.^[31] Tail immersion method is very much like to the tail flick method as both include heat stimuli for the action of pain but differ in the type of heat.^[32] In the tail, flick heat source is the coil and in tail immersion, hot water is used as a stimulus. Breaks of the procedure are the same. The experimental animal was kept in the cage and only one-third of the tail is allowable to come outside and then deepen in 51-55°C hot water bath until rat withdraws its tail, this is reaction time to stimuli and it is noted down. The cut out time is about 180 sec to prevent injury.^[33]

Procedure

- In the used for the experimental weight and number of rats/mice.

- The animals were divided into three groups- (1) Reference (2) Control (3) Experimental Groups.
- The reaction time is noted down of rat by sinking its tail in 51-55°C warm water.
- A cut off time will be about 120 sec to avoid unnecessary pain and damage.
- Inject the drug (Plant extract) on experimental animal and allow the drug to be absorbed, and over again place them to thermal stimulus basis and note down the basal reaction time.^[26-29]
- Before and after Insert medicine compare the response time.

B.) Stimulation of Hollow Organ

All the resources and methods described earlier used to measure the intensity of pain and efficacy of analgesic drug of outer pain and sometimes Central pain, this model is truly made for the visceral pain.^[34]

Procedure

- The allogeneic substance like formalin, acetic acid is directly injected into the hollow organ of the animal, this produces complex pain like body stretching and contraction of the body.
- This type of analgesic drugs was used to evaluate by in this procedure of analgesic pain.
- This method is significant as it includes the valuation of that type of pain, which are related to the internal organ, as sometimes the actual reason of internal pain is not known.

C.) Monkey Shock Test

Weiss gave this test in 1958 and then used by several researchers with little modification.

Procedure

- In this method, the monkey is allowed to seat in the chair and electrical current is delivered through coulbum instrument programmable shocker through the electrode, which is attached to the shaved tail of the monkey.
- The intensity of the current change from zero to four-mili ampere for about 29 steps.
- The monkey presses a bar to interrupt the flow of current and to get relief from the pain produced by that current.
- A point of pain is stabilized so that the evaluation of analgesic activity of drug may be determined by a change in the maximum level of median shock intensity that can be withstood by the animal.^[35]

CONCLUSION

These reviews try to make accessible an overview of reported analgesic activities of plants with of models in-vivo analgesic activities. The Based on the literature survey and detailed study of analgesic evaluation models it is concluded that every model is based on different parameter and principle so not all analgesic medicine can be evaluated on the same model. It's all of the various models of analgesic the most important in studying activity for analgesic drugs when this beneficial in human life.

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CONSTRUCTION OF REFERENCES

The authors whose names are listed immediately below report the following details of affiliation or involvement in an organization or entity with a financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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