International Journal of Medical and Health Research
ISSN: 2454-9142; Impact Factor: RJIF 5.54
Received: 12-08-2018; Accepted: 15-09-2018
www.medicalsciencejournal.com
Volume 4; Issue 10; October 2018; Page No. 128-130

Assessment of analgesic effect of gentamicin in comparison with aspirin thermally induced pain models in rats and mice

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Abstract
Gentamicin which is an aminoglycoside antibiotic has known to compete with Cellular calcium influx in several biological processes and it has been proven beyond doubt that it is an N- type calcium channel blocker. The present study was planned with the aim to compare the analgesic effect of Gentamicin with the renowned analgesic drug aspirin in thermally induced Pain models of rats and mice.
In our study, with regard to tail flick method, gentamicin at 160 µg dose showed a higher antinociceptive activity compared to aspirin at 60 min and 120 min in rats and at 90 min and 120 min in mice which indicates that it has a persistent analgesic action that might be explained due to its long duration of action.
From the above data generated it can be concluded that gentamicin is showing the comparable analgesic effect as that of aspirin in the tail flick method when administered to rats and mice. The study also concluded that the analgesic effect of the antibiotics can be used to supplement the other analgesic drugs thus minimising the adverse effect in some populations.

Keywords: analgesic effect, gentamicin, aspirin, thermally induced pain etc.

Introduction
Chronic pain is pain that lasts a long time. In medicine, the distinction between acute and chronic pain is sometimes determined by an arbitrary interval of time since onset; the two most commonly used markers being 3 months and 6 months since onset, though some theorists and researchers have placed the transition from acute to chronic pain at 12 months. Others apply acute to pain that lasts less than 30 days, chronic to pain of more than six months duration, and subacute to pain that lasts from one to six months. A popular alternative definition of chronic pain, involving no arbitrarily fixed duration, is "pain that extends beyond the expected period of healing". Epidemiological studies have found that 10.1% to 55.2% of people in various countries have chronic pain [1].
Chronic pain may originate in the body, or in the brain or spinal cord. It is often difficult to treat. Various non-opioid medicines are recommended initially, depending on whether the pain originates from tissue damage or is neuropathic. Psychological treatments including cognitive behavioural therapy and acceptance and commitment therapy may be effective for improving quality of life in those with chronic pain. Some people with chronic pain may benefit from opioid treatment while others are harmed. A trial of opioids is only recommended in those with non-cancer pain who have no history of either mental illness or substance use disorder and should be stopped if not effective [2].
Severe chronic pain is associated with increased 10 year mortality, particularly from heart disease and respiratory disease. People with chronic pain tend to have higher rates of depression, anxiety, and sleep disturbances; these are correlations and it is often not clear which factor causes another. Chronic pain may contribute to decreased physical activity due to fear of exacerbating pain, often resulting in weight gain. Pain intensity, pain control, and resiliency to pain are influenced by different levels and types of social support that a person with chronic pain receives.
Under persistent activation nociceptive transmission to the dorsal horn may induce a pain wind-up phenomenon. This induces pathological changes that lower the threshold for pain signals to be transmitted. In addition it may generate non-nociceptive nerve fibres to respond to pain signals. Non-nociceptive nerve fibres may also be able to generate and transmit pain signals. The type of nerve fibres that are believed to propagate the pain signals are the C-fibres, since they have a slow conductivity and give rise to a painful sensation that persists over a long time. In chronic pain this process is difficult to reverse or eradicate once established. In some cases, chronic pain can be caused by genetic factors which interfere with neuronal differentiation, leading to a permanent reduction in the threshold for pain [3].
Chronic pain of different etiologies has been characterized as a disease affecting brain structure and function. Magnetic resonance imaging studies have shown abnormal anatomical and functional connectivity, even during rest involving areas related to the processing of pain. Also, persistent pain has been shown to cause grey matter loss, reversible once the pain has resolved [4].
Gentamicin, sold under brand names Garamycin among others, is an antibiotic used to treat several types of bacterial infections. This may include bone infections, endocarditis, pelvic inflammatory disease, meningitis, pneumonia, urinary tract infections, and sepsis among others. It is not effective for gonorrhea or chlamydia infections. It can be given

intravenously, by injection into a muscle, or topically. Topical formulations may be used in burns or for infections of the outside of the eye. In the developed world it is often only used for two days until bacterial cultures determine what antibiotics the infection is sensitive to. The dose required should be monitored by blood testing [5].

Gentamicin which is an aminoglycoside antibiotic has known to compete with Cellular calcium influx in several biological processes and it has been proven beyond doubt that it is an N-type calcium channel blocker. The present study was planned with the aim to compare the analgesic effect of Gentamicin with the renowned analgesic drug aspirin in thermally induced Pain models of rats and mice.

Methodology

The study was planned in Department of Pharmacology, Anugrah Narayan Magadh Medical College. The study was conducted on Albino mice and Wistar rats of both the sexes. The animals were procured from the external animal house. The animals were treated as per the standard laboratory protocol. The study was approved by institutional ethical committee.

A total of 20 mice and 20 rats were distributed into four groups of 5 each:

Table 1

Study Groups	Drug Administered
Control Group	Distilled water
Group I	Gentamicin- low dose (80 µg/kg)
Group II	Gentamicin- high dose (160 µg/kg)
Group III	Aspirin (25 mg/kg in rats; 20 mg/kg in mice)

All drugs were given intraperitoneally.

Tail flick method

This experiment was carried out on rats and mice using analgesiometer devised by M.L. Gujral (Techno) which consists of nichrome wire, water jacket, switch, ammeter, low high control, pilot light, and a metallic rat holder. The nichrome wire which gives the radiant heat was arranged on the top of apparatus at a distance of about 0.25 cm below the level of water jacket which serves as a platform for the tail of the animal.

The animal under test was placed in a suitable metallic cylindrical holder with a perforated front piece and a specially arranged cut hole for the tail in the shutter. When the tail of animal is rested on the water jacket platform, it is switched on. All the animals were tested for noting the latent period of the withdrawal of tail after exposure to the radiant heat from the red hot wire of the analgesiometer. The current was adjusted so that tail withdrawal by all the animals on exposure to the red-hot wire was within 3-5 s. If the reaction time exceeded more than 10 s, it was assumed that complete analgesia had been produced. Further delay might cause tissue injury influencing the sensation. The animals were tested at 0, 30, 60, 90, and 120 min time intervals and results noted. The percentage increase in the mean reaction time (MRT) which indicates the degree of analgesia produced was calculated using the following formula.

$$\text{Percentage increase in MRT} = \frac{\text{MRT in test/standard} - \text{MRT in control}}{\text{Mean time in control}} \times 100$$

Result & discussion

From the data generated in the current study indicates that the analgesic effect of gentamicin in Tail flick method in rats and mice. The analgesic effect of Gentamicin is compared and proved against the reference drug Aspirin. Aspirin is considered as the standard drug for treatment for thermally induced pain.

In our study, with regard to tail flick method, gentamicin at 160 µg dose showed a higher antinociceptive activity compared to aspirin at 60 min and 120 min in rats and at 90 min and 120 min in mice which indicates that it has a persistent analgesic action that might be explained due to its long duration of action.

Table 2: Tail flick response in rats

Study Groups		0 Min	30 Min	60 Min	90 Min	120 Min
Control Group	-	3.1-3.5	3.95-4.6	3.4-3.6	4.1-4.6	3.6-4.6
Group I	80 µg/kg	3.5-3.9	7.5-8.9	3.5-3.6	7.5-8.7	7.6-9.5
Group II	160 µg/kg	3.4-3.8	7.2-8.8	4.1-4.3	8.6-9.6	8.4-9.6
Group III	20 mg/kg	3.6-4.0	8.6-9.7	4.2-4.4	8.9-9.4	7.3-8.6

Table 3: Tail flick response in mice

Study Groups		0 Min	30 Min	60 Min	90 Min	120 Min
Control Group	-	3.2-3.3	3.29-3.35	3.46-3.53	3.38-3.45	3.45-3.55
Group I	80 µg/kg	3.25-3.35	3.36-3.44	3.45-3.55	3.41-3.59	3.56-3.65
Group II	160 µg/kg	3.2-3.32	3.46-3.56	4.10-4.28	4.28-4.40	4.16-4.27
Group III	20 mg/kg	3.28-3.36	3.36-3.45	4.25-4.38	4.15-4.27	4.05-4.16

The tail flick and hot plate models have conventionally been used to study centrally acting analgesics [6]. Although both methods employed thermal stimuli, as mentioned earlier, the tail-flick response indicates spinally mediated reflex while the paw-licking hot plate response is due to complex supraspinal integrated behaviour. Findings from our study demonstrated that gentamicin prolonged the reaction time in the tail-flick method but showed an apparent lack of effect in the hot plate method. This might indicate a higher sensitivity of the spinally mediated reflex response in the tail-flick method.

The possible mechanism of our findings is - gentamicin being an aminoglycoside antibiotic has reduced the synaptosomal

calcium availability by acting as an N-type calcium channel blocker and thus decreases neuronal activity [7-9] indicating antagonism between calcium and aminoglycoside antibiotics [10]. Nociception has been hypothesized to be related to the calcium levels inside the neurons [11]. Since it has been shown that calcium is involved in the action of opioids [12], it may be that calcium influences pain perception mediated by opioid receptors also [13].

Conclusion

From the above data generated it can be concluded that gentamicin is showing the comparable analgesic effect as that of aspirin in the tail flick method when administered to rats and mice. The study also concluded that the analgesic effect of the antibiotics can be used to supplement the other analgesic drugs thus minimising the adverse effect in some populations.

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