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RESEARCH ARTICLE

Evaluation of analgesic effect of Gentamicin in thermally induced pain models in rats and mice

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ABSTRACT

Background: Evidence has accumulated for the involvement of calcium ions in nociception and N-type voltage-dependent calcium channels being critical for pain transduction and modulation. N-type calcium channel blockers represent a new class of analgesics that are selective for calcium channels involved in pain signal transmission. Gentamicin, an aminoglycoside antibiotic was discovered to block these N-type voltage-dependent calcium channels. **Aims and Objectives**: The present study is to evaluate the analgesic activity of gentamicin in thermally induced pain models of rats and mice and compare it against the standard analgesic aspirin. **Materials and methods**: A total of 24 rats and 24 mice were distributed into four groups of 6 each: Group A received distilled water as control, Group B received Gentamicin- low dose (80 µg/kg), Group C received Gentamicin- high dose (160 µg/kg), and Group D received standard drug Aspirin (20 mg/kg in rats and 25 mg/kg in mice); all drugs were given intraperitoneally. Analgesic activity was determined using tail flick method and hot plate method. In both the methods, the mean reaction time (MRT) in seconds at 0, 30, 60, 90, and 120 min among the four groups were noted in both rats and mice. The percentage increase in MRT was calculated which indicates the degree of analgesia produced. **Results**: In the tail flick test, increase in the MRT was statistically significant ($P < 0.05$) in Group B, Groups C and D at all the time intervals except 0 min in rats, whereas in mice, it was highly significant ($P < 0.001$) in only Groups C and D. In hot plate method, in rats, the increase in MRT was statistically significant ($P < 0.05$) at 90 and 120 min in Group C and at 60 min in Group D, whereas it was highly significant at 90 min in Group D. In mice, increase in MRT was found to be significant at 90 min in Group B, at 60 and 120 min in Group C and at 120 min in group D whereas it was highly significant at 90 min in Group C and at 60 and 90 min in Group D. **Conclusion**: Gentamicin showed a comparable analgesic activity to aspirin in tail flick method but lower analgesic activity in hot plate method in both rats and mice.

KEY WORDS: Hot Plate Method; Mean Reaction Time; N-type Calcium Channels; Tail Flick Method

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INTRODUCTION

Chronic pain is usually defined as any pain which lasts for 3-6 months or longer. The prevalence estimates for chronic pain range from 9% to 33%[1,2] and these figures are expected to increase due to advances in health care that will continue to prolong the lifespan of patients. It not only effects the quality

of life but also inadequate management of chronic pain has profound social, economical and psychological impacts.

Evidence has accumulated for the involvement of calcium ions in nociception and antinociception.[3-5] N-type voltage-dependent calcium channels are critical for pain transduction and modulation. These channels are highly present at the synaptic terminals and dorsal root ganglia cell bodies that make dorsal horn of the spinal cord.[6,7] These primary afferents which constitute mainly C and A-δ fibers are implicated in the sensation of a variety of noxious painful stimuli.

Critically, block of these N-type channels prevents the release of neurotransmitters like glutamate and substance-P. Consistent with this, the selective blockers of the N-type channels are powerful analgesics, and mice lacking the N-type Calcium channels have higher pain thresholds compared to wild-type.[8] N-type calcium channel blockers are being considered of having therapeutic potential in chronic pain management.[9]

Gentamicin which is an aminoglycoside antibiotic has known to compete with Cellular calcium influx in several biological processes[10] and it has been proven beyond doubt that it is an N- type calcium channel blocker.[11]

The analgesic drugs introduced so far are associated with some considerable side effects namely euphoria, depressant action on vital centers, addiction, tolerance, etc. Therefore, search for a new, potent, safe, and nontoxic drug continues. In the present work, gentamicin has been compared with a standard drug aspirin for its analgesic property mainly in thermally induced Pain models of rats and mice.

MATERIALS AND METHODS

Animals

Albino mice weighing 20-30 g and Wistar rats weighing 150-250 g of either sex were used in this study. The animals were procured from the central animal house of our institute. They were housed in cages in standard laboratory conditions with natural light and dark cycle and at room temperature. Food and water were given *ad libitum*. The study protocol was approved by the Institutional ethics committee and care of the animals was as per the "Guidelines for the care and use of laboratory animals."

Drugs and Chemicals

Gentamicin (Genticyn) 80 mg injection manufactured by Abbott Healthcare Pvt. Ltd. and Aspirin (Ecospirin) 75 mg tablet manufactured by USV limited were used in this study. All drug solutions were freshly prepared in double distilled water at room temperature.

Experiment Protocol

A total of 24 mice and 24 rats were distributed into four groups of 6 each:

1. Group A received distilled water as control
2. Group B received Gentamicin- low dose (80 µg/kg)
3. Group C received Gentamicin- high dose (160 µg/kg)
4. Group D received standard drug Aspirin (25 mg/kg in rats; 20 mg/kg in mice)

All drugs were given intraperitoneally.

Assessment of Analgesic Activity

For assessing the analgesic activity, two thermal methods were used namely Tail flick method[12] and hot plate method.[13] In both the methods, rats and mice were first screened to eliminate nonresponders, animals which do not show any kind of response in the tests due to their inherent nature.

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.

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

Hot plate method

The experiment was conducted in rats and mice using hot plate method devised by Eddy and Leimbach (1953). Hot plate analgesia apparatus (Techno) is a thermostatically controlled electrically heated plate heated by a thermode

or a boiling liquid surrounded by a transparent square box (22×22×15 cm) with flexible lid on its top. A plate heated to a constant temperature produces two behavioral components that can be measured in terms of their reaction times, namely paw licking and jumping. Animal was placed gently on the hot plate through upper lid and the stopwatch was immediately pressed on. The animal was visualized carefully through the transparent wall for noting the characteristic cut off responses. As soon as the animal responded to noxious stimulus, the stopwatch was shut off and the animal was taken away from the hot plate. The time interval between the threshold cut off response and on placing the animal on a hot plate, as measured in seconds by stopwatch, was taken as the threshold reaction time to induce pain to noxious stimulus.

The paws of both rats and mice are very sensitive to temperature at 55 ± 0.5C which are not damaging to the skin. The response is in the form of jumping, withdrawal of the paws or licking of the paws. The animals were placed on the eddy's hot plate maintained at temperature of 55 ± 0.5C. A cutoff period of 15 s was observed to avoid damage to the paw in mice and 20 s in rats. Reaction time and response were noted using a stopwatch. The animals were tested, and the results were noted at 0, 30, 60, 90, and 120 min time intervals. Percentage increase in the MRT which indicates the degree of analgesia produced was calculated using the following formula.

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

Statistical Analysis

All the results are presented in mean±standard error of mean (SEM) and in percentage protection in test and standard groups in comparision to control group. Statistical analysis of data was performed using Students' *t*-test to study the differences among the means. A $P < 0.05$ is considered significant and <0.001 is considered highly significant.

RESULTS

Table 1 shows the results of Tail flick response in rats denoted by reaction time in seconds as mean ± SEM at different time intervals. At 0 min (immediately after giving the drug), Gentamicin at 80 µg, and 160 µg showed an increase in the MRT by 12.2% and 9.09% compared to control whereas with Aspirin, it increased by 15.5%. At 30 min, Gentamicin at 80 µg/kg and 160 µg/kg showed an increase in MRT by 92.94% and 88.23% when compared to control, whereas with aspirin, it increased by 115.52% (Figure 1).

At 60 min, Gentamicin at 80 µg/kg and 160 µg/kg showed an increase in MRT by 92.30% and 136.29% when compared to control, whereas with aspirin, it increased by 124.27%. At 90 min, Gentamicin at 80µg/kg and 160 µg/kg showed an increase in MRT by 86.04 and 111.62% when compared to control, whereas with aspirin, it increased by 116.27%. At 120 min, Gentamicin at 80µg/kg and 160 µg/kg showed an increase in MRT by 114.63 and 119.51% when compared to control, whereas with aspirin, it increased by 95.12%. All MRTs for both doses of Gentamicin and the standard dose of aspirin are significant ($P < 0.05$) at all-time intervals except at 0 min (Figure 1).

Table 2 shows the results of Tail flick response in mice denoted by reaction time in seconds as mean ± SEM at different time intervals. At 0 min, Gentamicin at 80 µg/kg and 160 µg/kg showed an increase in MRT by 0.92% and 0.92% compared to control, whereas with aspirin, it increased by 1.22%. At

Table 1: Tail flick response in rats

Group	Dose	Reaction time in seconds at different time intervals				
		0 Min	30 Min	60 Min	90 Min	120 Min
A (Control)	-	3.30±0.21	4.25±0.40	4.16±0.30	4.30±0.30	4.10±0.50
B (Gentamicin)	80 µg/kg	3.70±0.25	8.20±0.70*	8.00±0.70*	8.00±0.70*	8.80±0.80*
C (Gentamicin)	160 µg/kg	3.60±0.23	8.00±0.80*	9.83±0.20*	9.10±0.50*	9.00±0.60*
D (Aspirin)	20 mg/kg	3.80±0.17	9.16±0.50*	9.33±0.30*	9.30±0.40*	8.00±0.90*

All values are expressed as Mean±SEM, Min: Minutes, *P<0.05: Statistically significant, SEM: Standard error of mean

Table 2: Tail flick response in mice

Group	Dose	Reaction time in seconds at different time intervals				
		0 Min	30 Min	60 Min	90 Min	120 Min
A (Control)	-	3.27±0.06	3.32±0.03	3.49±±0.03	3.41±0.03	3.50±0.04
B (Gentamicin)	80 µg/kg	3.30±0.05	3.40±0.04	3.51±0.04	3.50±0.07	3.60±0.05
C (Gentamicin)	160 µg/kg	3.30±0.05	3.51±0.05†	4.20±0.08†	4.32±0.04†	4.21±0.06†
D (Aspirin)	25 mg/kg	3.31±0.04	3.41±0.03	4.32±0.06†	4.21±0.06†	4.11±0.05†

All values are expressed as Mean±SEM, Min: Minutes, †P<0.001: Statistically highly significant, SEM: Standard error of mean

30 min, Gentamicin at 80 µg/kg and 160 µg/kg showed an increase in MRT by 2.41% and 5.72% when compared to control, whereas with aspirin it increased by 2.71% (Figure 2).

At 60 min, Gentamicin at 80 µg/kg and 160 µg/kg showed an increase in MRT by 0.57% and 20.34% when compared to control, whereas with aspirin it increased by 23.78%. At 90 min, Gentamicin at 80 µg/kg and 160 µg/kg showed an increase in MRT by 2.64% and 26.69% when compared to control, whereas with aspirin, it increased by 23.46%. At 120 min, Gentamicin at 80 µg/kg and 160 µg/kg showed an increase in MRT by 2.86 and 20.29% when compared to control, whereas with aspirin, it increased by 17.43%. Here, the increase in the MRT by Gentamicin at a dose of 160 µg/kg at all-time intervals is highly significant ($P < 0.001$), whereas the increase in the MRT for Aspirin is highly significant ($P < 0.001$) only at 60 min and 90 min (Figure 2).

Overall, gentamicin has comparable analgesic activity to aspirin in tail flick method in both rats and mice. Gentamicin has a quick onset of action with a prolonged duration when compared to aspirin.

Table 3 shows the results of hot plate method in rats as denoted by reaction time in seconds as mean ± SEM at different time intervals. At 0 min, Gentamicin at 80 µg/kg and 160 µg/kg showed an increase in MRT by 1.70% and 3.15% compared to control, whereas with aspirin, it increased by 13.09%. At 30 min Gentamicin at 80 µg/kg and 160 µg/kg showed an increase in MRT by 5.41% and 21.63% when compared to control, whereas with aspirin, it increased by 22.44% (Figure 3).

At 60 min, Gentamicin at 80 µg/kg and 160 µg/kg showed an increase in MRT by 36.22% and 25.85% when compared to control, whereas with aspirin, it increased by 102.32%. At 90 min, Gentamicin at 80 µg/kg and 160 µg/kg showed an increase in MRT by 29.48% and 43.89% when compared to control, whereas with aspirin, it increased by 49.35%. At 120 min, Gentamicin at 80 µg/kg and 160 µg/kg showed an increase in MRT by 16.96% and 43.12% when compared to control, whereas with aspirin, it increased by 26.41%. Here, the increase in the MRT by Gentamicin (160 µg/kg) is significant ($P < 0.05$) at 90 and 120 min and for aspirin at 60 min, and highly significant ($P < 0.01$) at 90 min, (Figure 3).

Table 4 shows the results of hot plate method in mice as denoted by reaction time in seconds as mean ± SEM at different time intervals. At 0 min, Gentamicin at 80 µg/kg and 160 µg/kg showed an increase in MRT by 1.24% and 10.26% compared to control, whereas with aspirin it increased by 12.28%. At 30 min, Gentamicin at 80 µg/kg and 160 µg/kg showed an increase in MRT by 3.67 and 25.72% when compared to control, whereas with aspirin, it increased by 22.30%. At 60 min, Gentamicin at 80 µg/kg and 160 µg/kg showed an increase in MRT by 28.22% and 31.14% when compared to control, whereas with aspirin, it increased by 35.88%.

At 90 min Gentamicin at 80 µg/kg and 160 µg/kg showed an increase in MRT by 34.25% and 41.79% when compared to control, whereas with aspirin it increased MRT by 48.98%. At 120 min Gentamicin at 80 µg/kg and 160 µg/kg showed an increase in MRT by 31.90 and 38.28% when compared to control, whereas with aspirin it increased MRT by 47.85%. Here, the increase in the MRT is significant ($P < 0.05$) for Gentamicin (80 µg/kg) at 90 min, Gentamicin (160 µg) at 60 and 120 min and for aspirin at 120 min. The increase in the MRT is highly significant ($P < 0.001$) for Gentamicin (160 µg) at 90 min and for aspirin at 60 and 90 min (Figure 4).

In this method, analgesic effect of gentamicin was more when compared to control in rats and mice but less when compared with aspirin.

DISCUSSION

In this study, we evaluated the analgesic action of gentamicin, an aminoglycoside antibiotic using two thermal methods namely Tail flick method and hot plate method in rats and mice. The analgesic action was compared with aspirin, which is considered as the standard drug for treating 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. The tail-flick response is believed to be a spinally mediated reflex and the effectiveness

Table 3: Results of hot plate method in rats

Group	Dose	Reaction time in seconds at different time intervals				
		0 Min	30 Min	60 Min	90 Min	120 Min
A (Control)	-	8.25±1.56	8.69±1.06	8.20±0.78	12.28±1.11	11.85±1.46
B (Gentamicin)	80 µg/kg	8.39±1.17	9.16±1.25	11.17±1.81	15.90±1.05	13.86±2.07
C (Gentamicin)	160 µg/kg	8.51±0.82	10.57±1.06	10.32±0.74	17.67±1.65*	16.96±1.65*
D (Aspirin)	25 mg/kg	9.33±1.05	10.64±1.27	16.59±3.02*	18.34±1.51†	14.98±0.94

All values are expressed as Mean±SEM, Min: Minutes, *P<0.05: Statistically significant, †P<0.001: Statistically highly significant, SEM: Standard error of mean

of analgesic agents in the tail-flick pain model is highly correlated with relief of human pain perception. The tail-flick method is based on the observation that morphine-like compounds are selectively able to prolong the reaction time of typical tail-withdrawal effect in rats.[14] This method is also useful in differentiating central opioid-like analgesics from peripheral analgesics.[15]

In hot plate method, gentamicin at 160 µg dose was found inferior to aspirin in its antinociceptive activity at majority of time intervals both in rats and mice. The paw-licking hot plate response is a complex supraspinally organized behavior.[16] Hot plate method produces two measurable behavioral components in response to thermal pain with regard to their reaction times. Responses such as paw licking and jumping in rats are considered to be supraspinally integrated. Thus, the failure of both doses of gentamicin to inhibit these behaviors on hot plate method indicates that it might not be acting at supraspinal level.

The tail flick and hot plate models have conventionally been used to study centrally acting analgesics.[17] 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 supraspinally integrated behavior. 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. However, intra-animal variation may also contribute to the lack of effect in hot plate method. Unlike the typical tail withdrawal reflex, problem arises in the hot plate method

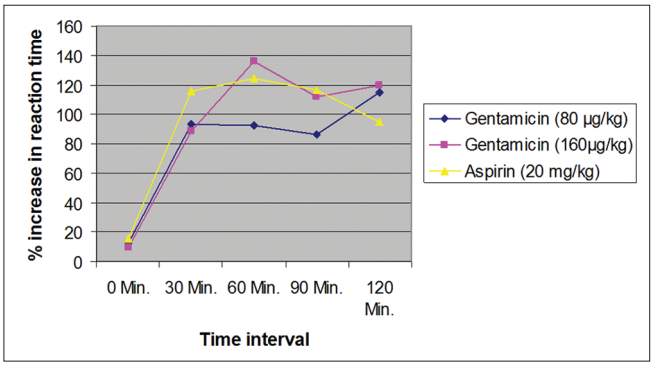

Figure 1: Percentage increase of mean reaction time in tail flick method in rats

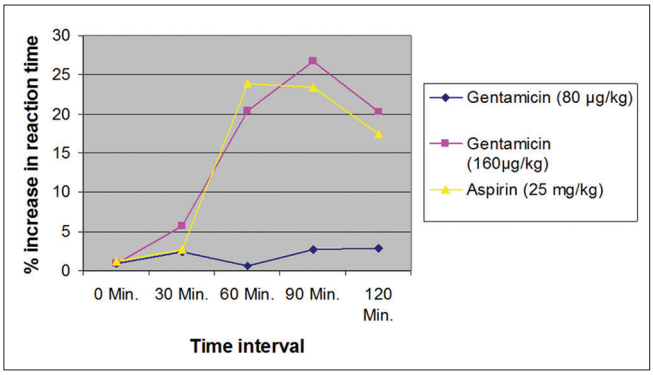

Figure 2: Percentage increase of mean reaction time in tail flick method in mice

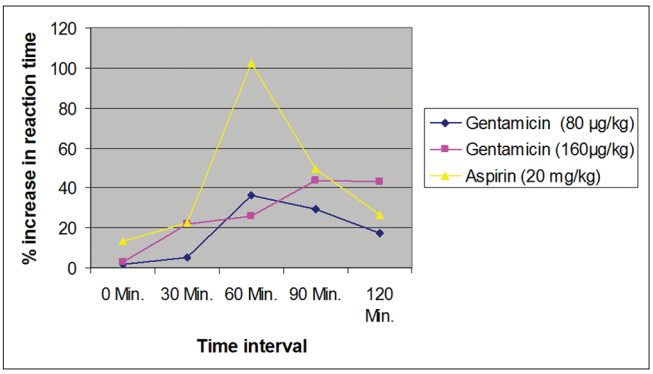

Figure 3: Percentage increase of mean reaction time in hot plate method in rats

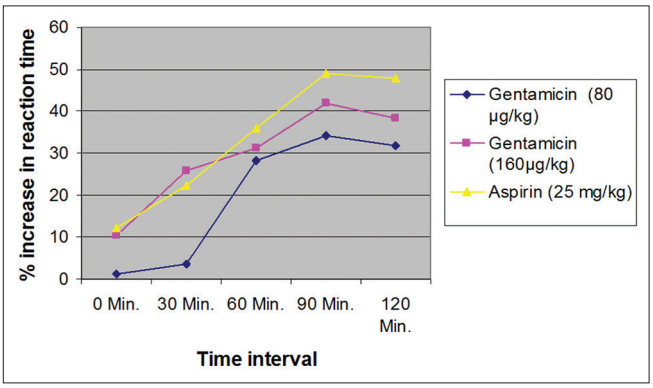

Figure 4: Percentage increase of mean reaction time in hot plate method in mice

Table 4: Results of hot plate method in mice

Group	Dose	Reaction time in seconds at different time intervals				
		0 Min	30 Min	60 Min	90 Min	120 Min
A (Control)	-	6.43±1.37	7.89±1.25	8.22±0.78	8.35±1.05	8.15±0.97
B (Gentamicin)	80 µg/kg	6.51±1.62	8.18±1.03	10.54±1.32	11.21±1.28*	10.70±1.11
C (Gentamicin)	160 µg/kg	7.09±1.18	9.92±1.68	10.78±1.81*	11.84±2.06†	11.27±1.23*
D (Aspirin)	25 mg/kg	7.22±0.98	9.65±1.16	11.17±1.33†	12.44±1.69†	12.05±2.35*

All values are expressed as Mean±SEM, Min: Minutes, *P<0.05: Statistically significant, †P<0.001: Statistically highly significant, SEM: Standard error of mean

as the animals have to learn what nociceptive response they need to show to stop the thermal stimulus.[18] Taken together, the differences in sensitivity of both methods as well as the mechanism involved may explain the analgesic effects observed in our study.

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[19-21] indicating antagonism between calcium and aminoglycoside antibiotics.[10] Nociception has been hypothesized to be related to the calcium levels inside the neurons.[22] Since it has been shown that calcium is involved in the action of opioids,[23] it may be that calcium influences pain perception mediated by opioid receptorsa also.[24]

Strengths of our study include selecting two thermal methods which are the standard methods of screening analgesics, performing the study in two species and as gentamicin is one the most commonly used antibiotic in government setup in India, demonstrating its analgesic effect can be used to supplement other analgesic drugs whose dose and thereby their adverse effects can be effectively reduced. Our study had some limitations such as shorter duration, the inconsistency seen with tail flick response due to habituation and finally pain being subjective in nature and it is difficult to comment on the effectiveness of an analgesic purely on the basis of animal studies, an inherent limitation of all animal studies of pain.

CONCLUSION

In our study, gentamicin showed a comparable analgesic activity to aspirin in tail flick test both in rats and mice but in hot plate method it showed lower analgesic activity. In both the methods, it showed significantly higher analgesic response compared to control.

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