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STUDY OF ANTI INFLAMMATORY ACTIVITY OF RIFAMPICIN AND ISONIAZID IN WISTAR RATS

Pharma

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ABSTRACT

Background: Inflammation accompanies many infections, including tuberculosis (TB). Rifampicin and Isoniazid, key anti-TB drugs, have shown conflicting anti-inflammatory effects in previous studies. **Objective:** To evaluate the anti-inflammatory activity of Rifampicin and Isoniazid in Wistar rats using models of acute and chronic inflammation. **Methods:** Anti-inflammatory effects were assessed using carrageenan-induced paw edema, turpentine-induced arthritis, and cotton pellet granuloma models. Ibuprofen served as the standard. **Results:** Ibuprofen showed significant anti-inflammatory activity. Rifampicin increased inflammatory markers across all models, suggesting a proinflammatory effect. Isoniazid showed no significant anti-inflammatory activity. **Conclusion:** Rifampicin and Isoniazid may exhibit proinflammatory actions; further studies are required.

KEYWORDS

INTRODUCTION

Inflammation is a complex reaction to various injurious agents such as infections, trauma, foreign bodies, tissue necrosis, physical, and chemical agents that consists of vascular responses, migration and activation of leukocytes and systemic reactions.(Kumar et al., 2010)

India is a country with highest T.B burden, it nearly accounts for 1/5th of the global burden. The pathogenesis of TB involves a combination of immune and inflammatory process. (Gandigawad et al.,2015)

Rifampicin and Isoniazid is considered most effective drug for control of tuberculosis, some studies has shown that rifampicin an isoniazid also possess anti-inflammatory activity. Rifampin increases nitric oxide production.(Yuhas et al., 2005) and also increases cytokine induced expression of the CD1b molecule in human peripheral blood monocytes. Also it decreases the concentration of TNF-α and transcription nuclear factor β2, which is involved in immunostimulation. (Tentori et al.,1998)

Apart from studies on Rifampicin isoniazid has been also shown to possess antiinflammatory activity by decreasing the levels of Interleukin-2.(Pahlevan, 2002)

So this study is planned to understand anti-inflammmatory action of Rifampicin and Isoniazid in wistar rat on different model of acute and chronic inflammation.

MATERIALAND METHOD MATERIALS:

1) Animals: Healthy adult albino rats of either sex weighing between 150-200 grams were used in the experiment. The Study was conducted after approval from the Institutional Animal Ethics Committee. The Study was performed in accordance with the CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals) guidelines.

2) Drugs and Chemicals: Rifampicin, Isoniazid, and Ibuprofen (pure powder) and chemicals such as gum acacia, carrageenan, turpentine oil, and diethyl ether were procured from Ozone Chemicals, Mumbai. Fresh drug solutions were prepared in 1% gum acacia half an hour before the experiment. Carrageenan (1% in 0.9% saline) was administered at 0.1 ml per paw.

3)Animal Grouping: Rats were divided into four groups (n = 6): Control (gum acacia, 2 ml), Ibuprofen (100 mg/kg), Rifampicin (54 mg/kg), and Isoniazid (27 mg/kg), all orally.

4) Equipment: Digital plethysmometer, electronic vernier caliper, cotton pellets, forceps, and electronic balance.

Experimental Methods:

1) Carrageenan Induced- Rat Paw Oedema:(Gandigawad et al.,2015, Attia, 2015, Lalan,2015)

Each rat's paw was marked at the lateral malleolus. After oral drug administration, 0.1 ml of 1% carrageenan (in saline) was injected intradermally into the right hind paw. Paw volume was measured using a mercury plethysmometer at baseline and hourly intervals up to 4 hours. The difference in paw volume was calculated by subtracting the baseline reading from the 4-hour reading. Anti-inflammatory activity was assessed by comparing the mean difference in paw volume between control and drug-treated groups. Percentage inhibition was calculated using the formula: % inhibition

$$\text{Percentage inhibition} = \frac{(C-T)}{C} X100 \text{.(Lalan,2015)}$$

Where, C= Mean increase in paw volume in the control group
T= Mean increase in paw volume in the drug treated group

2) Turpentine Induced- Arthritis In Rats:

Each rat's knee joint was marked with ink. One hour after oral drug administration, 0.05 ml of turpentine oil was injected into the right knee joint to induce acute inflammation (Singh et al., 2011). Lateral knee diameter was measured using a digital vernier caliper at zero hour and four hours post-injection (Suresh et al., 2009). The change in diameter was calculated by subtracting the zero-hour value from the 4-hour value. Statistical analysis compared the mean diameter change between control and treated groups. Percentage inhibition of inflammation was calculated using the formula:

$$\text{Percentage inhibition} = \frac{(C-T)}{C} X100 \text{.(malviya et al., 2009)}$$

C= Mean increase in lateral diameter of knee joint in the control group
T= Mean increase in lateral diameter of knee joint in the drug treated group.

3) Cotton Pellet Granuloma In Rats

On day 1, test drugs were administered orally. Rats were lightly anesthetized with ether, and the axillary skin was disinfected using 70% ethanol. Two sterile cotton pellets (10 mg each) were implanted through 1 cm incisions made near each axilla, and the wounds were sutured. Animals were housed in clean cages with aseptic precautions, and drug administration continued for six consecutive days ((Majagi et al.,2006). On day 11, rats were re-anesthetized with diethyl ether, and pellets with surrounding granulation tissue were removed. The wounds were resutured and animals were allowed to recover. Pellets were cleaned, dried in a hot air oven at 60°C for 18 hours (Y.R et al., 2017), and weighed to determine the dry granuloma weight. The difference between the pre- and post-implantation weights was calculated. Statistical analysis compared the mean granuloma weights

between groups. Anti-inflammatory activity was expressed as:

$$\% \text{ Inhibition} = \frac{(Wc-Wt)}{Wc} X\ 100$$ ((Gandigawad et al.,2015))

Wc = Mean dry weight of granuloma in the control group Wt = Mean dry weight of granuloma in the drug treated group

RESULTS

1) Carrageenan Induced Rat Paw Edema

Table 1: Change in paw volume compared to basal and there % inhibition in Carrageenan induced rat paw oedema

Drug group	Basal		Difference with basal (mm) in				% Inhibtion			
	Mean	SEM (±)	1 hr	2 hr	3 hr	4 hr	1hr	2hr	3hr	4hr
Control	1.27	0.10	0.18	0.19	0.16	0.11	-	-	-	-
Ibuprofen	1.13	0.06	0.06	0.04	0.28	0.18	64.51	77.94	-78.88	-60.3
Isoniazid	0.99	0.11	0.37	0.41	0.40	0.33	-98.92	-112.8	-152.7	-186.2
Rifampicin	0.98	0.07	0.55	0.38	0.49	0.45	-195.6	-98.46	-204.3	-289.6

Isoniazid is showing proinflammatory activity to a quite an extend like – 152.7% and -186.2% on third and fourth hours respectively as compared to control.

Similarly rifampicin is showing proinflammatory activity to a much more extent as can be seen in table, it is even more then Isoniazid.

A paired t-test was used to analyze the differences in paw edema among the treatment groups. The standard anti-inflammatory drug, Ibuprofen, showed a statistically significant reduction in paw volume when compared to the control group (mean difference = 0.125 ± 0.048, p = 0.015), indicating effective anti-inflammatory activity in the acute inflammation model.

Rifampicin also demonstrated a statistically significant difference from the control group (mean difference = 0.122 ± 0.058, p = 0.047). However, based on earlier observations of increasing paw volume following Rifampicin administration, this difference is suggestive not of an anti-inflammatory effect, but rather a proinflammatory response.
In contrast, Isoniazid did not show a statistically significant difference from the control group (mean difference = 0.079 ± 0.064, p = 0.227), indicating that it neither reduced nor significantly influenced the paw edema in this model. This suggests that Isoniazid lacks measurable anti-inflammatory or proinflammatory activity under the experimental conditions used.

When comparing Ibuprofen to Isoniazid, no significant difference was observed (mean difference = -0.046 ± 0.058, p = 0.435), indicating that although Ibuprofen was effective, the variability within groups may have reduced the statistical power to detect a difference. Similarly, there was no significant difference between Ibuprofen and Rifampicin (mean difference = -0.003 ± 0.052, p = 0.955), suggesting that despite their opposing trends (anti-inflammatory vs. proinflammatory), the net difference was not large enough to reach statistical significance.

The comparison between Isoniazid and Rifampicin also did not show a significant difference (mean difference = 0.043 ± 0.070, p = 0.548), implying that both drugs produced a comparable, mild, or inconsistent inflammatory response in the acute setting.

In conclusion, Ibuprofen demonstrated a clear and statistically significant anti-inflammatory effect. Rifampicin, despite showing statistical significance versus control, appears to exert a proinflammatory effect based on its associated increase in paw volume. Isoniazid showed no significant impact, neither anti-inflammatory nor proinflammatory. These findings provide important insights into the inflammatory profiles of these drugs, particularly the potential proinflammatory nature of Rifampicin in acute inflammation.

2) Turpentine Induced Arthritis

Table 2: Change in knee joint diameter as compared to basal and there % inhibition in Turpentine induced arthritis

Drug group	Basal		Difference with basal (mm) in				% Inhibtion			
	Mean	SEM (±)	1hr	2hr	3hr	4hr	1hr	2hr	3hr	4hr
Control	7.083	0.144	0.75	0.9	1.46	1.46	-	-	-	-
Ibuprofen	8.233	0.178	0.45	0.15	0.58	0.46	40	83.33	60.19	68.16
Isoniazid	7.700	0.154	0.35	0.4	0.48	0.88	53.33	55.55	67.07	43.21
Rifampicin	7.150	0.092	0.533	1.21	1.53	2.05	28.93	-35.22	-7.90	-39.74

Table 2 showed that Ibuprofen has greater anti-inflammatory activity. Isoniazid reduced inflammation compared to control but less than Ibuprofen. Rifampicin increased knee swelling beyond control levels, indicating a proinflammatory effect.

Comparison Between The Groups In Turpentine-induced Arthritis

As estimated by the paired t-test, a significant difference was observed between several test and control group comparisons. The standard drug (Ibuprofen) showed a significant anti-inflammatory effect compared to the control group (mean difference = -0.573 ± 0.210, p = 0.011), confirming its expected efficacy. Rifampicin also showed a statistically significant difference when compared to control (mean difference = -0.226 ± 0.093, p = 0.022). However, as observed from the percentage inhibition values and the direction of change, this difference is attributed to a proinflammatory response rather than anti-inflammatory activity.

In contrast, Isoniazid did not show a statistically significant difference from the control group (mean difference = -0.133 ± 0.115, p = 0.257), indicating minimal to no anti-inflammatory effect in this model.

When comparing standard vs Isoniazid, a significant difference was noted (mean difference = 0.440 ± 0.138, p = 0.004), further emphasizing the lack of anti-inflammatory activity of Isoniazid.

The difference between standard and Rifampicin (p = 0.128) and between Isoniazid and Rifampicin (p = 0.490) were not statistically significant.

Overall, the paired t-test results support a significant difference between test and control groups, and the data indicate that Rifampicin may exert a proinflammatory effect in the turpentine-induced arthritis model.

3) Cotton Pellet Induced granuloma

Table 3 : Mean Dry Weight Of Cotton Pellet

	MEAN	SD	SE(±)
Control	55.40	6.85	2.80
Ibuprofen	48.95	4.83	1.97
Isoniazid	59.32	8.77	3.58
Rifampicin	59.50	10.13	4.13

Comparison Between The Groups Of Cotton Induced Granuloma

In the chronic inflammation model using cotton pellet-induced granuloma, the mean dry weight of granuloma tissue was used as an indicator of inflammation. The analysis revealed that the Ibuprofen-treated group showed a statistically significant reduction in granuloma weight compared to the control group (mean difference = 6.45 ± 2.17, p = 0.031), confirming its anti-inflammatory efficacy in chronic inflammation.

In contrast, both Rifampicin and Isoniazid groups did not show statistically significant differences when compared to the control group (Rifampicin: p = 0.447; Isoniazid comparisons: p > 0.05). Moreover, the mean dry weights in both these groups were slightly higher than that of the control, suggesting a tendency toward a proinflammatory effect rather than an anti-inflammatory action.

Comparisons between Ibuprofen and Isoniazid (p = 0.475), as well as Ibuprofen and Rifampicin (p = 0.096), did not reach statistical significance but showed a trend indicating that the standard drug (Ibuprofen) was more effective in reducing granuloma formation. The comparison between Isoniazid and Rifampicin (p = 0.101) also

showed no significant difference, but the near-equal and elevated mean values of dry weight in both groups again reflect a lack of anti-inflammatory potential.

Overall, these results demonstrate that Rifampicin and Isoniazid may contribute to chronic inflammatory responses, indicating possible proinflammatory activity in this model.

DISCUSSION

In our study, Isoniazid and Rifampicin demonstrated proinflammatory activity across all tested models. Isoniazid showed negative % inhibition in carrageenan-induced rat paw edema, indicating inflammation, contrasting with Priya Gandigawad et al. who reported anti-inflammatory effects (63.95% inhibition at 3rd hour) and reduced granuloma weight (26.17 g vs. 40.67 g control) (Gandigawad et al.,2015). Rifampicin also showed negative inhibition values and increased granuloma weight (59.32 g vs. 55.4 g control), suggesting a proinflammatory trend. Supporting this, Kucharz EJ et al., observed low doses of Isoniazid enhanced IL-2 production, implying immune activation [Kucharz et al., 1995]. Tentori and Graziani demonstrated that Rifampicin upregulated CD1b expression in monocytes, promoting antigen presentation [Tentori et al., 1998]. Though some studies suggested mild anti-inflammatory effects (Gandigawad et al.,2015, Spain et al., 1952) the overall trend in our study indicates a proinflammatory effect, especially with increased cytokine responsiveness and immune cell activation. Given these contrasting findings, further research is warranted to elucidate the exact immunomodulatory role of Isoniazid and Rifampicin in inflammation and wound healing.

CONCLUSION

Our study concludes that Isoniazid and Rifampicin are having proinflammatory activity, which is more for Rifampicin than Isoniazid. However from previous studies there are lots of controversy still remaining if the drugs are pro or anti-inflammatory, so further studies are required to support the true nature of the drugs.

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