Shenoy *et al*.

EFFECTS OF SODIUM IODIDE ON INFLAMMATION AND ITS INTERACTION WITH ASPIRIN AND MEFENAMIC ACID IN ALBINO RATS

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Summary

Objective: To investigate the effects of sodium iodide on acute and sub-acute inflammation in albino rats and to explore its interaction with aspirin and mefenamic acid Methods: Sodium iodide was evaluated for its antiinflammatory action by carrageenan induced and foreign body induced inflammation in albino rats. The combinations of sodium iodide + aspirin and sodium iodide + mefenamic acid were also investigated for their effects on inflammation. **Results:** Sodium iodide potentiated anti- inflammatory activity of aspirin and mefenamic acid in acute inflammation. In sub-acute model, sodium iodide (SAI dose) when combined with aspirin 54 mg/kg b.w. failed to show the significant anti- inflammatory activity. Similarly, sodium iodide failed to potentiate anti- inflammatory of mefenamic acid (SAI dose) and the mean granuloma dry weight was 16.46±2.17mg.

Conclusion: Sodium iodide in its therapeutic (400mg/ day) equivalent dose showed significant anti- inflammatory activity in the acute model of inflammation.

Keywords: Sodium iodide, aspirin and mefenamic acid

Introduction

Inflammation, a common clinical condition is said to a complex protective reaction in the vascularised be connective tissue due to variety of exogenous and endogenous stimuli causing cell injury and is characterized by the reaction of blood vessels, leading to accumulation of fluids and leukocytes in extravascular tissue.¹ Though the process of inflammation is brought about by vascular as well as cellular events, the former appears to contribute maximum for the pathogenesis of acute inflammation. This complex phenomenon involves endogenous chemical mediators histamine, 5- hydroxy tryptamine, various such as factors, bradykinin, leukotrienes chemotactic and prostaglandins.²

Many NSAIDs like aspirin, phenylbutazone, indomethacin, etc. are in clinical use but all of these are not completely devoid of adverse effects. Hence, the search continues for safer, better anti- inflammatory agents other than NSAIDs. Agents like calcium channel blockers, zinc, adrenergic agonists and antagonists have shown to be possessing anti- inflammatory activity.^{3,4}

Similarly, iodides have been reported to be useful in the treatment of variety of conditions like gout, rheumatism, neuralgias, etc.,⁵ possibly due to their antiinflammatory activity. However, mechanism of antiof activity iodides inflamatory was not. explained.Paradoxically iodides have also been shown to flare up the inflammatory process in tubercular and lesions⁵ suggesting its proinflammatory gummatous potential. In fact, beneficial effects of iodides in the treatment of sporotrichosis have been attributed to its pro- inflammatory activity.6

Subsequent experimental study has shown that sodium iodide in acute model of inflammation (mouse ear oedema) exerted its anti- inflammatory activity by scavenging oxidant radicals released during PGG_2 reduction.⁷ However, there is a paucity of information regarding anti-inflammatory action of iodides in sub- acute inflammation.

Despite earlier literature regarding antiinflammatory activity of iodides, presently they are rarely used in the clinical practice for such purpose. They are mainly used topically as antiseptics or for the treatment of skin conditions like sporotrichosis. Occasionally, they may be used systemically for treatment of simple goitre of for preparing thyroid gland for surgery. Reduced vascularity of the thyroid goitre by iodides when used pre-

aspirin and mefenamic acid.

surgically could also be expected and thereby contributing to the anti- inflammatory activity of iodides in variety of conditions like gout, rheumatism, neuralgias, etc as reported earlier.⁵ Therefore, the present study is aimed at investigating the effects of sodium iodide on carrageenan induced (acute) and foreign body induced (subacute) inflammation in albino rats. Since iodides are consumed in minute quantities through diet, it is worth investigating for its possible interaction with OTC drugs, particularly NSAIDs which are frequently consumed. Hence the present study also aims to explore its interaction with some commonly used NSAIDs like

Methods

Adult albino rats of either sex were procured from the central animal house and kept on standard pellets and water *ad libitum*. They were starved overnight with free access to water prior to the day of experiment and were divided into control and different treatment groups (n=6 in each group)

Carrageenan induced rat paw oedema (acute model):

Acute inflammation was induced by injecting carrageenan (0.1 ml of 1% suspension in 0.9% saline) in sub- plantar region and paw volume was measured at 0, 1, 2, 3, 4 and 5 hours, with the help of plethysmometer (UGO Basile, Italy) After grouping separately, each group was orally administered with one of the following treatments.

- 1. Aspirin 200mg/kg
- 2. Mefenamic acid 45mg/kg
- 3. Sodium iodide 36mg/kg
- 4. Aspirin 54 mg/kg + sodium iodide 27mg/kg
- 5. Mefenamic acid 2.25mg/kg + sodium iodide 27 mg/kg

All the treatments were administered 30 mins prior to carrageenan. Acute inflamation was induced in each group by injecting 0.1 ml of 1% carrageenan into the subplantar region of right hind paw. A mark was put on the leg at the malleolus to facilitate the dipping of the leg to the same level at the second and subsequent times.

The initial reading was taken as zero hour, that is immediately after injecting carrageenan and the procedure was reported at one, two, three, four and five hours after carrageenan injection. The difference between zero hour reading and one of the subsequent readings provides the actual oedema volume at that time. The mean paw volume at different times was calculated for all groups and the percentage inhibition was then calculated by using the formula; % inhibition = 1- (V_t / V_c) x 100 Where V_t = the amount of oedema formed in drug treated group V_c = the amount of oedema formed in the control group The results were analyzed by ANOVA followed by Dunnet's test (p value< 0.05 was taken as significant)</pre>

Foreign body induced granuloma method (subacute model):

The method of D'Arcy et al ⁸ was adopted with some modification. Thirty six albino rats were divided into six groups (n=6 in each). Under light ether anaesthesia, the hair over groin and axilla were clipped and cleaned with alcohol. Under aseptic precautions through small incisions two sterilized cotton pellet of 10 mg each and two sterilized grass piths were implanted at random. The wounds were closed with the help of sterilized silk and animals were housed individually after recovering from anaesthesia

Food and water were withheld for 4 hours after the above procedure and subsequently allowed freely.

Each group was administered one of the treatments, similar to the groups in acute study. However the treatment was started after implanting foreign bodies and was repeated every 24 hours for 10 days.

On the 11th day, the rats were sacrificed by over anaesthesia and pellets and grass piths covered with granulation tissue were dissected out. Each pellet was removed of fat and extraneous tissue and dried overnight at 60°C. The weight of the individual pellets were noted and the net amount of granuloma were quantified by subtracting 10mg from this weight. The mean granuloma dry weight for various groups was calculated and expressed as mg/100G body weight.

The rats which were divided into six groups were administered various drugs and their combinations as described earlier for a period of 10 days (including the day of implantation) continously once in a day at the

same time i.e. 10 am to 11 am. All the animals were kept in clean cages.

The group mean was calculated for all the groups and compared with the control. Statistical analysis was done by ANOVA followed by Dunnet's test.

The dissected grass piths were immediately kept in 10% formalin and subjected later for the histopathological studies. The granulation tissue preserved in 10% formalin was processed in the department of Pathology, and sections were stained with haematoxylin and eosin. Quantification of granulation tissue in each groups was done microscopically

Drugs and chemicals

Sodium iodide	Loba Chemie private limited
Aspirin	Ashok pharmaceuticals
Mefenamic acid	Bluecross company
Carrageenan	US Sigma

Results

Carrageenan induced acute inflammation:

The control group at 0.5h, 1h, 2h, 3h, 4h and 5h had oedema volume of 13.58 ± 1.97 ml, 27.28 ± 3.98 ml, 39.8 ± 5.39 ml, 51.23 ± 6.44 ml, 40.56 ± 4.86 ml and 36.60 ± 5.21 ml respectively. The corresponding mean volume in aspirin (200mg/kg, b.w) treated group were 13.15 ± 2.43 ml at 0.5h, 21.95 ± 3.62 ml at 1h, 18.29 ± 3.76 ml at 2h, 15.53 ± 4.17 ml at 3h, 22.89 ± 2.78 ml at 4h and 24.73 ± 2.83 ml at 5h. However the significant anti- inflammatory activity of aspirin was observed at 2^{nd} hour and lasted till 4^{th} hour after carrageenan.

Mefenamic acid in the dose of 45mg/kg (table 1) showed significant inhibition of paw oedema (p<0.01- 0.001) at 1h, 2h, 3h, 4h and 5h with mean oedema volume of 8.71±3.20ml, 4.53±1.15ml, 11.11±9.01ml, 9.9±1.89ml, 8.82±2.31ml respectively. These results indicate that compared to that of aspirin, mefenamic acid has earlier onset and longer duration of anti- inflammatory activity. Sodium iodide in the dose of 36mg/kg (table1) showed significant inhibition of paw oedema (p<0.01) at 0.5h, 1h, 2h, 3h and 4h with mean oedema volume of 5.56±1.37 ml, 11.91±2.14 ml, 24.62±2.53 ml, 28.97±2.16 ml and 23.81±2.86 ml respectively. To study possible interactions between aspirin, mefenamic acid and sodium iodide, a series of experiments were carried out to determine sub anti- inflammatory doses (SAI) of sodium iodide and mefenamic acid. Accordingly, the SAI dose for sodium iodide was found to be 27mg/kg and 2.25 mg/kg for mefenamic acid. Mean paw volume for SAI dose of sodium iodide was 8.97±1.78 ml, 18.72±3.96 ml, 32.36±2.63 ml, 53.1±5.35 ml, 44.57±6.17 ml and 34.9±6.1 ml respectively for 0.5h, 1h, 2h, 3h, 4h and 5h. Similarly, the mean paw volume of mefenamic acid (2.25 mg/kg) was 18.7±2.05ml at 0.5h, 33.16±4.64 ml at 1h, 44.5±6.59 ml at 2h, 50.7±5.03 ml at 3h, 46.57±4.75 ml at 4h and 33.1±4.64 ml at 5 h

SAI dose of aspirin (54mg/kg) when given with sodium iodide 27mg/kg showed significant inhibition (p<0.05) of inflammation.(table 1)

Mefenamic acid in the dose of 2.25mg/kg when coadministered with SAI dose of sodium iodide showed significant anti- inflammatory activity.

These results clearly indicate that sodium iodide potentiated anti- inflammatory activity of aspirin and mefenamic acid used in the model of acute inflammation induced by carrageenan

Sub- acute inflammation (foreign body induced granulomas):

Sterile cotton pellet induced granulomas dry weight was expressed as mg per 100g body weight. Aspirin and mefenamic acid showed significant anti- inflammatory activity (p<0.001; p<0.01 respectively); however sodium iodide when compared to control did not show significant (p<0.5) reduction in granulomas dry weight (Table 2).

The mean dry weight of 10 day old granulomas in control animals was 13.98±1.23mg, while it was significantly (p<0.001) decreased in aspirin (200mg/kg) treated animals with the mean value of 6.33 ± 0.62 mg. Similarly, mefenamic acid (45mg/kg) also showed significant (p<0.01) decrease granulomas dry weight with the mean value of in 9.30±0.65mg. Sodium iodide in the dose of 36 mg/kg did show significant suppression of the granuloma not formation and the mean granulomas dry weight was 15.84±1.02mg (Table 2).

These observations indicate the anti- inflammatory activity of aspirin and mefenamic acid. Unlike in acute studies, sodium iodide (SAI dose) when combined with aspirin 54 mg/kg b.w. failed to show the significant anti- inflammatory activity and the mean granuloma dry

weight was 13.89±0.58mg. Similarly, sodium iodide failed to potentiate anti- inflammatory of mefenamic acid (SAI dose) and the mean granulomas dry weight was 16.46±2.17mg.

The effect of various treatments on granulomas formation was further confirmed by histopathological studies of haematoxyline and eosin stained granulation tissue sections in the various treated groups. There was abundant granulation tissue (macroscopically) surrounding the grass pith in control animals and microscopic studies revealed reduced number of fibroblasts, decreased collagen content and fibrous tissue in aspirin (200mg/kg), mefenamic acid 45mg/kg treated groups as compared to saline treated control. The histological picture of granulation tissue in animals treated with sodium iodide alone and in combination with aspirin or mefenamic acid was almost similar to that of control group.

Shenoy et al.

Table 1: Effect of various treatments on carrageenan induced rat paw oedema

Group	Drug and oral	Paw volume in ml (Mean ±SE)					
(n=6)	dose/kg b.w.	0.5	1 hr	2 hr	3 hr	4 hr	5 hr
		hr					
1.	Control(1%gum	13.5	27.28	39.8	51.23	40.56	36.60
	acacia)	8	±3.98	±5.39	±6.44	±4.86	±5.12
		±1.9					
		7					
2.	Aspirin 200mg/kg	13.1	21.95	18.29**±3	15.53	22.89	24.73
		5	±3.62	.76	* * *	* *	±2.83
		±2.4			±4.17	±2.78	
		3					
3.	Mefenamic acid	7.23	8.71*	4.53**±1.	11.11	9.9**	8.82*
	45mg/kg	±0.7	*±3.2	15	* *	±1.89	*
		1	0		±9.01		±2.31
4.	Sodium iodide	5.56	11.91*	24.62*±2.	28.97	23.81	12.37
	36mg/kg	**±1	*	53	* *	*	±3.11
		.37	±2.14		±2.16	±2.86	
5.	Mefenamic acid	18.7	33.16	44.5±6.59	50.7	46.57	33.1
	2.25mg/kg	±2.0	±4.64		±5.03	±4.75	±4.64
		5					
6.	Sodium iodide	8.97	18.72	32.36±2.6	53.1	44.57	34.9
	27mg/kg	±1.7	±3.96	3	±5.35	±6.17	±6.10
		8					
7.	Sodium iodide	11.3	17.13	17.05**	29.17	21.23	16.00
	2/mg/kg + Aspirin	4	±2.89	±3.18	*	*	*
	54mg/kg	±1.9			±6.60	±5.17	±4.41
					F 001	4 851	F 001
8.	Sodium iodide	4.10	3.62*	2.85***	5.82*	4.75*	5.90*
	2/mg/kg + Metenamic	**	**	±0.99	**		
	acid 2.25mg/kg	±0.7	±1.09		±2.49	±1.75	±0.77

Anova $F_{7,40}$ = 7.76 (0.5h), 8.34 (1h), 16.86 (2h), 11.74 (3h), 14.72 (4h) and 9.55 (5h) > 4.85; p=0.001 *p<0.05, **p<0.01, ***p<0.001 (Dunnet's test)

Shenoy et al.

Table 1. Elleet el valleab eleatmente en felergi beag inadead granatema								
Group(n=)	Drug and dose	Mean granuloma	8	`t'	`p'			
		dry	inhibition	value	value			
		weight(mg/100g						
		b.w)						
1.	Control	13.98±1.23						
2	Aspirin(200mg/kg)	6.33±0.62	54.8	5.51	<0.001			
3	Mefenamic acid(45mg/kg)	9.30±0.65	34.0	3.33	<0.01			
4	Sodium iodide(36mg/kg)	15.84±1.02	13.0	1.16	<0.5			
5	Sodium	13.89±0.58	1.0	0.06	p>0.5			
	<pre>iodide(27mg/kg)+Aspirin(54mg/kg)</pre>							
6	Sodium iodide(27mg/kg)+Mefenamic	16.46±2.17	17.0	0.99	p>0.5			
	acid(2.25mg/kg)							

Table 2: Effect of various treatments on foreign body induced granuloma

ANOVA $F_{5,30} = 11.18 > 4.84; p = 0.001$







Figure 2: Aspirin



Figure 3: Mefenamic acid

Shenoy et al.



Figure 4: Sodium iodide



Figure 5: Sodium iodide and aspirin



Figure 6: Sodium iodide and mefenamic acid

Note: Granuloma mass, vascularity, fibroblast number and collagen content is significantly decreased in figure 2 and 3 compared to figure 1. Granuloma mass, vascularity, fibroblast number and collagen content is not significantly decreased in figure 4, 5 and 6.

Discussion

As mentioned in the introduction, the aim of the present study was to investigate the influence of sodium iodide on acute as well as sub- acute inflammation in albino rats and also elicit their possible interactions with commonly used NSAIDs like aspirin and mefenamic acid. As expected, both aspirin as well as mefenamic acid in therapeutic equivalent doses showed significant antiinflammatory activity in both the models of inflammation used in the present study.

In the present study, sodium iodide in its therapeutic (400mg/ day) equivalent dose showed significant antiinflammatory activity in the acute model of inflammation. The present findings are in agreement with the earlier model observation that sodium iodide in acute of inflammation (mouse ear oedema) exerted antiinflammatory activity. In contrast to the findings of the present study, earlier studies have reported the proinflammatory activity of iodides when used in sporotrichosis and gummatous lesions.

The discrepancy regarding the effects of iodides on inflammation appears to be related with the duration of inflammation and cause of inflammation. In the present study, the SAI dose of sodium iodide potentiated the anti- inflammatory activity of aspirin and mefenamic acid in acute model of inflammation. Such an interaction of sodium iodide with NSAIDs appears to be poorly documented.

Similarly, in sub- acute model of inflammation, both aspirin and mefenamic acid produced significant anti- inflammatory activity. However, sodium iodide not only alone, but also in combination with aspirin and mefenamic acid failed to elicit significant antiinflammatory activity.

There is paucity of information regarding its action on sub- acute model of inflammation. This was further confirmed by histopathological studies.

The aim of the present study was not to probe into the mechanism of anti- inflammatory activity of sodium iodide. However, based on the earlier reports,⁶ it could be attributed to activities like dissolving and clearing gummata and to assist in the resolution of the inflammation and cause absorption of morbid products and serous exudates⁹. It could be speculated that sodium iodide might have inhibitory activity on mediators of acute inflammation. To what extent such an activity contributes for its observed anti- inflammatory activity is difficult to assess.

The interaction between sodium iodide and aspirin or mefenamic acid appears to be of pharmacodynamic nature rather than $pharmacokinetic^{10}$.

The findings of the present study if could be extrapolated to the clinical situation, the patients on iodide therapy may require smaller dose of NSAIDs to suppress acute inflammation. However, this needs to be confirmed by clinical studies.

Acknowledgement

The authors are grateful to the Principal, J. N. Medical College, Belgaum for providing facilities and Dr. P. R. Malur, Professor of Pathology for his guidance in microscopic studies. I also thank Mr. Mallapur, Biostastician, Mr. A. V. Karvekar and Mr. M. D. Kankanwadi for their skilful assistance.

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