MODULATION OF ANTI-INFLAMMATORY ACTIVITY OF NSAIDS IN NORMAL RATS TREATED WITH ANTIHISTAMINICS.

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ABSTRACT: NSAIDs are frequently used for relief of inflammation and Antihistaminics are indicated for simultaneous administration for allergic manifestations. Opioids analgesics have been reported to interact with Antihistaminics. To explore the interacting potentiality, in the present study the effects of combined treatment with NSAIDs and antihistaminics were examined in rats. Anti-inflammatory effect was evaluated by Carrageenan induced hind paw oedema in rats. NSAIDs like aspirin, ibuprofen and piroxicam were selected for study on per se and on concurrent administration with Antihistaminics such as Promethazine, Cetrizine and Astemizole. All NSAIDs protected animals show anti-inflammatory activity. Aspirin shows highly significant potentiation of anti-inflammatory effect at all dose level, however ibuprofen and piroxicam show highly significant anti-inflammatory effect at higher doses only and on concurrent administration of antihistaminics, aspirin, piroxicam and ibuprofen with all antihistaminics produced highly significant potentiation except ibuprofen with Cetrizine produced significant potentiation of anti-inflammatory response at higher doses only.
KEY WORDS: antihistaminics, inflammation, NSAIDs drug interaction

INTRODUCTION: Plethora of drugs available to the physicians and frequent need of several drugs for concurrent use has resulted in increased frequency of drug interaction. Use of multiple drugs concurrently, in practice of medicine, and excess of drugs available to the physicians, has resulted in increased frequency of drug interactions.

It is presumed that drug interactions comprise about 7.0% of all adverse reactions and that among the few patients who succumb to adverse drug reactions (about 4.0% of all deaths) about a third are due to interactions (1).

Genetic or environmental factors, intercurrent illness or polypharmacy might affect the response of concurrently administered drug combinations.

All NSAIDs protected animals show anti-inflammatory activity. Aspirin shows highly significant potentiation of anti-inflammatory effect at all dose level, however ibuprofen and piroxicam show highly significant anti-inflammatory effect at higher doses only and on concurrent administration of aspirin, piroxicam and ibuprofen with all antihistaminics

produced highly significant potentiation except ibuprofen with Cetrizine produced significant potentiation of anti-inflammatory response at higher doses only.

AIMS AND OBJECTIVES:

1. To explore anti-inflammatory effects of NSAIDs per se.
2. To explore the drug interacting potentiality on concurrent administration of NSAIDs with antihistaminics.

MATERIAL AND METHODS: Anti-inflammatory effect was evaluated by Carrageenan induced hind paw oedema in rats (2). This study was conducted in Albino rats of either sex with ten rats in each group weighing (100-200 gms). Rats were maintained under standard laboratory conditions in animal house of M.L.B. medical college Jhansi, U.P. India. The rodents had access to food and water. The study was permitted by institutional animal ethical committee. One group was treated with 2ml/kg distilled water served as control while other groups were treated with drugs with three dose level of each drug. All the drugs used in this study were given in suspension of 2% gum acacia orally except promethazine which were administered intramuscularly. The inflammation was induced by subcutaneous injection 0.1ml 1.0% Carrageenan suspension in the planter aponeurosis of right hind paw. The oedema resulting after 3 hours of Carrageenan injection was measured by plethysmometer (3). The hind paw oedema was noted as paw volume. The difference between the paw volume before and 3 hours after Carrageenan injection was recorded as volume of paw oedema. The drugs administered orally as suspension in 2.0 % gum acacia except prometazine one hour before Carrageenan injection. The percentage inhibition of oedema volume (anti-inflammatory effect) was calculated by the following formula:-

$(1- V_t/V_c \times 100)$

Where V_t= volume of paw oedema in treated rats

V_C = volume of paw oedema in control rats.

Statistical analysis is done by using paired t- test.

RESULTS:

Table- 1 Anti-inflammatory effect of non – opioid analgesics on Carrageenan induced oedema

S.No.	Group	No. Of animals	Dose (mg/kg)	Carrageenan induced oedema volume (ml) (Mean ± S.E.)	(% inhibition)
1	Control (distilled water)	10	2 ml	.64±.01	-
2	Aspirin	10	50	.54±.003***	16
			100	.44±.01***	32
			200	.34±.01***	47
3	ibuprofen	10	50	.60±.005*	7
			100	.56±.018**	13
			200	.48±.01***	25
4	piroxicam	10	0.29	.60±.003*	7
			0.58	.55±.09***	15
			1.16	.49±.01***	24

*P < .05 **P < .01 ***P <.001

Table-2. Anti-Inflammatory effect of Aspirin with Antihistaminics on Carrageenan induced oedema –

S.No.	Group	No. Of animals	Dose (mg/kg)	Carrageenan induced oedema volume (ml) (Mean ± S.E.)	(% inhibition)
1	Control (distilled water)	10	2 ml	0.64±0.009	-
2	Aspirin+ Cetrizine	10	50+1.60	0.57±0.008***	11
			100+3.20	0.48±0.01***	25
			200+6.40	0.36±0.01***	44
3	Aspirin+Astemizole	10	50+1	0.50±0.005***	22
			100+2	0.46±0.01***	29
			200+4	0.32±0.007***	50
4	Aspirin+Promethazine	10	50+1	0.55±0.01***	15
			100+2	0.49±0.01***	24
			200+4	0.42±0.007***	35

*P<0.05 **P<0.01 ***P<0.001

Table-3. Anti-inflammatory effect of ibuprofen with Antihistaminics on Carrageenan induced oedema –

S.No.	Group	No. Of animals	Dose (mg/kg)	Carrageenan induced oedema volume (ml) (Mean ± S.E.)	(% inhibition)
1	Control (distilled water)	10	2 ml	0.88±0.01	-
2	Ibuprofen+Cetrizine	10	50+1.60	0.74±0.01	16
			100+3.20	0.66±0.01***	25
			200+6.40	0.52±0.01***	41
3	Ibuprofen+Astemizole	10	50+1	0.72±0.006***	19
			100+2	0.55±0.01***	38
			200+4	0.45±0.01***	49
4	Ibuprofen+Promethazine	10	50+1	0.71±0.003***	20
			100+2	0.61±0.006***	31
			200+4	0.54±0.008***	39

*P<0.05 **P<0.01 ***P<0.001

Table- 4. Anti-inflammatory effect of piroxicam with on Carrageenan induced oedema –

S.No.	Group	No. Of animals	Dose (mg/kg)	Carrageenan induced oedema volume (ml) (Mean ± S.E.)	(% inhibition)
1	Control (distilled water)	10	2 ml	0.67±0.009	-
2	Piroxicam+Cetrizine	10	0.29+1.60	0.57±0.003***	15
			0.58+3.20	0.51±0.01***	24
			1.16+6.40	0.40±0.008***	41
3	Piroxicam+Astemizole	10	0.29+1	0.53±0.009***	21
			0.58+2	0.49±0.006***	27
			1.16+4	0.42±0.008***	38
4	Piroxicam+Promethazine	10	0.29+1	0.54±0.01***	20
			0.58+2	0.51±0.008***	24
			1.16+4	0.42±0.008***	38

*P<0.05 **P<0.01 ***P<0.001

RESULTS: Anti-inflammatory effect (% inhibition) of oedema volume was evaluated by Carrageenan induced oedema volume in (ml) (mean ± SE) in the control group (0.64±0.01) no % inhibition on per se administration of NSAIDs used in this study, aspirin showed highly significant % inhibition in oedema and ibuprofen and piroxicam showed significant inhibition of oedema at higher doses only (Table1.)

On concurrent administration of all NSAIDs with Cetrizine, Astemizole and Promethazine produced highly significant ($P < 0.001$) % inhibition of oedema volume except Ibuprofen with Cetrizine at low dose does not produce 0.74 ± 0.01 significant % inhibition of oedema volume. (Table-3)

Concurrent administration of aspirin with all antihistaminics produced highly significant % inhibition of oedema ($p < 0.001$) (Table-2) and concurrent administration of ibuprofen with Astemizole and promethazine produced highly significant activity ($p <0.001$) except ibuprofen with Cetrizine at low dose does not produce % inhibition of oedema (0.74 ± 0.01) (table-3). Piroxicam with Cetrizine, Astemizole and promethazine produced highly significant effect ($p <0.001$). Interaction of piroxicam with Cetrizine, Astemizole and promethazine used in this study was evaluated by % inhibition of oedema volume at 3 dose levels as compared to control in table-4.

DISCUSSION: Enhanced toxicity or decreased therapeutic effects resulting from administration of drug combinations have recently gained tremendous importance in therapeutic practice. Drug interaction between opioid analgesics and phenothiazine, monoamine oxidase inhibitors and tricyclic antidepressants is well established (4).

Superior analgesic and comparable anti-inflammatory property with gastrointestinal sparing effect with zinc –naproxen complex when impaired with naproxen alone (5).

Both Phenylybutazone and Aspirin enhanced Glibenclamide induced hypoglycaemia (6). (Diwan et al 1992) showed potentiation of hypoglycaemic response of Glibenclamide by Piroxicam (a newer NSAIDs) in rats, human volunteers and diabetics (7).

Potent anti-inflammatory activity of μ and kappa agonists and identification of selectin as important molecules governing the homing of opioid cells to injured tissue (8). Some opioid analgesics have anti-inflammatory activity but little information is availed about NSAIDs and antihistaminic interaction.

In this study per se administration of NSAIDs aspirin shows highly significant % inhibition of oedema. Ibuprofen and Piroxicam showed significant inhibition of oedema at higher doses only. On concurrent administration of all NSAIDs with H1 blockers produced highly significant ($P < 0.001$) % inhibition of oedema except ibuprofen with Cetrizine which produced significant effect at higher doses only.

All NSIADs have protected animals effectively although aspirin was most potent which confirm the possessions of NSAIDs anti-inflammatory activity by these drugs. On per se administration of NSAIDs in which aspirin produced highly significant anti-inflammatory activity and ibuprofen and piroxicam produce significant anti-inflammatory activity only at higher dose level and with concurrent administration of antihistaminics, all NSAIDs produce highly significant anti-inflammatory activity. However ibuprofen with Cetrizine produces highly significant anti-inflammatory activity at higher doses only.

In view of these observations it can be safely concluded that antihistaminics possess interaction potentiality with NSAIDs. So caution should be taken in use of these drugs on concurrent administration in clinical practice.

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