# PHARMACOLOGICAL STUDY OF ULCEROGENIC ACTION OF ANTIPYRETIC ANALGESIC AGENTS AND THEIR INTERACTION WITH SODIUM SALICYLATE

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**Summary :** The present work was undertaken to study and compare the gastric ulcerogenic action of analgesic antipyretic agents in guinea pigs. Their interaction with sodium salicylate was also studied. It was observed that aspirin, both microfined and ordinary, phenylbutazone, indomethacin and sodium salicylate were highly ulcerogenic in guinea pigs, while paracetamol and ibuprofen did not exhibit this action. It was also observed that sodium salicylate did not modify the ulcerogenic action of aspirin (both ordinary and microfined), phenylbutazone, ibuprofen and paracetamol but antagonized significantly the ulcerogenic action of indomethacin.

**Key words :** ulcerogenic action analgesic antipyretic agents interaction

## INTRODUCTION

Many antipyretic analgesic agents induce gastric ulcers in laboratory animals and man (1,2,4,10). Antagonism of the gastric ulcerogenic effect of indomethacin, acetylsalicylic acid, niflumic acid and phenylbutazone by sodium salicylate has been shown after simultaneous oral administration in rats (5). It is also reported that salicylic acid given 1 or 3 hr after indomethacin administration decreases plasma concentration of indomethacin in rats (17). Interaction between salicylates and other non-steroidal anti-inflammatory drugs is reported in rats (3).

The present work was undertaken to compare gastric ulcerogenic action of antipyretic analgesics in guinea pigs. It was also decided to study interaction of these drugs with sodum salicylate. In order to elucidate the mechanism of ulcerogenic action, effect of these drugs on gastric acidity was also studied.

## MATERIAL AND METHODS

(I) *Gastric ulcerogenic activity :* Guinea pigs of either sex weighing 240 *gm* to 550 *gm* were used. The animals were kept fasting for 24 hr before the drug administration and they had free access to tap water during this period. They were housed individually in cages at room temperature with natural light cycle. Precautions were taken to avoid coprophagy. Ten animals were used for each drug. All drugs were suspended in 5 *ml* of 1% gum acacia solution, and were administered into the stomach through a stomach tube passed through oral cavity. After 6 hr of drug administration, the animals were sacrificed by giving a blow on the head. The abdomen was opened by midline incision and stomach was removed and cut along the greater curvature. Gastric mucosa was washed under running tap water and was examined for the presence of ulcers. The ulcer index for each animal was calculated by summing up the length in mm of all the ulcers (13); also mean number of ulcers and ulcer score per stomach were calculated (16). Drug interaction with sodium salicylate was studied by giving sodium salicylate 30 min before the drug administration.

(II) *Measurement of total acidity.*

The gastric contents were collected and centrifuged for 10 min.

Estimation was done by titrimetric method (7, 11). The following drugs were used: aspirin ordinary 200 *mg/kg*, aspirin microfined 200 *mg/kg*, indomethacin 20 *mg/kg*, phenylbutazone 100 *mg/kg*, ibuprofen 100 *mg/kg*, paracetamol 300 *mg/kg*, sodium salicylate 200 *mg/kg*.

The results were statistically analysed by applying student's 't' test.

## RESULTS

Aspirin both ordinary and microfined, indomethacin, phenylbutazone and sodium salicylate were ulcerogenic, while ibuprofen and paracetamol did not show significant ulcerogenic action (Table I).

(I) *Mean number of ulcers per stomach* :

When compared with control, the mean number of ulcers was raised significantly by both the preparations of aspirin, indomethacin and sodium salicylate. Sodium salicylate

TABLE I : Effect of drugs on gastric mucosa in guinea pigs.

| | Treatment | n=animals used | Dose mg/kg | Mean number of ulcers per stomach ± S.E. | Ulcer index ± S.E. | Mean ulcer score ± S. E. |
|---|---|---|---|---|---|---|
| 1. | Control | (10) | | 4.3±1.33 | 9.9±2.25 | 1.2±0.34 |
| 2. | Aspirin ordinary | (10) | 200 | 10.4±2.77 | 46.8±18.61 | 2.1±0.31 |
| 3. | Aspirin microfined | (10) | 200 | 13.3±3.5° | 47.6±11.35* | 2.8±0.36* |
| 4. | Indomethacin | (10) | 20 | 9.0±1.84 | 41.8±9.53* | 2.2±0.33° |
| 5. | Phenylbutazone | (10) | 100 | 4.7±1.11 | 21.2±5.77 | 1.4±0.22 |
| 6. | Ibuprofen | (10) | 100 | 2.5±0.67 | 7.1±2.49 | 0.9±0.18 |
| 7. | Paracetamol | (10) | 300 | 3.4±0.72 | 7.4±2.7 | 1.1±0.1 |
| 8. | Sodium salicylate | (10) | 200 | 8.9±0.94° | 36.2±5.82* | 2.3±0.20° |
| 9. | Sodium salicylate + aspirin ordinary | (10) | | 10.6±1.54 | 40.8±6.95 | 2.6±0.34 |
| 10. | Sodium salicylate + aspirin microfined | (10) | | 13.2±1.83 | 43.8±6.13 | 2.9±0.31 |
| 11. | Sodium salicylate+indomethacin | (10) | | 5.4±1.34 | 20.0±6.33 | 1.6±0.27 |
| 12. | Sodium salicylate + phenylbutazone | (10) | | 9.3±1.57° | 32.8±7.54 | 2.3±0.26° |
| 13. | Sodium salicylate+ibuprofen | (10) | | 9.4±1.95* | 31.6±6.34* | 2.3±0.39* |
| 14. | Sodium salicylate+paracetamol | (10) | | 11.3±1.33* | 35.5±7.07* | 2.5±0.27* |

°=P<0.05 * =P<0.01.

Groups 2 to 8 were compared with group no. 1.

Groups 9, 10, 11, 12, 13 & 14 were compared with Group no. 2, 3, 4, 5, 6 and 7 respectively.

produced no significant change in the mean number of ulcers per stomach in animals treated with aspirin (both ordinary and microfined) while reduction in the number of ulcers obtained by indomethacin approached significance when compared with aspirin and indomethacin alone respectively. Sodium salicylate enhanced significantly gastric ulcerogenic action of phenylbutazone, ibuprofen and paracetamol, when compared with individual drug (Table I).

(II) *Ulcer index* : The ulcer index was raised significantly by almost all drugs, except ibuprofen and paracetamol as compared with control. Prior treatment of animals

with sodium salicylates did not affect significantly the gastric ulcerogenic action of aspirin (both the preparations). While interaction with indomethacin significantly antagonized when this was compared with aspirin and indomethacin alone respectively. The index was potentiated significantly by ibuprofen and paracetamol interaction with sodium salicylate, when were compared with individual drug (Table I).

III) *Mean ulcer score* This was raised by drugs like aspirin (ordinary and microfined), indomethacin and sodium salicylate. The interaction of phenylbutazone, ibuprofen and paracetamol with sodium salicylate, raised mean ulcer score significantly compared with the score of each drug alone.

TABLE II : Effect of drugs on gastric acidity.

| | *Drug* | *n=animals used* | *Dose mg/kg* | *Total acidity mEq/lit* | *P value* |
|---|---|---|---|---|---|
| 1. | Control | (10) | | 80.6±5.72 | |
| 2. | Aspirin ordinary | (10) | 200 | 35.5±7.65 | 0.01 |
| 3. | Aspirin Microfined | (10) | 200 | 15.1±1.93 | 0.01 |
| 4. | Indomethacin | (10) | 20 | 38.5±8.93 | 0.05 |
| 5. | Phenylbutazone | (10) | 100 | 45.7±8.19 | 0.01 |
| 6. | Ibuprofen | (10) | 100 | 39.5±3.32 | 0.01 |
| 7. | Paracetamol | (10) | 300 | 37.5±6.16 | 0.05 |
| 8. | Sodium Salicylate | (10) | 200 | 27.2±3.7 | 0.01 |
| 9. | Sodium salicylate+aspirin ordinary | (10) | | 6.7±0.77 | 0.01 |
| 10. | Sodium Salicylate+aspirin microfined | (10) | | 6.8±0.42 | 0.01 |
| 11. | Sodium salicylate+indomethacin | (10) | | 19.7±5.35 | 0.1 |
| 12. | Sodium salicylate+phenylbutazone | (10) | | 10.00±2.82 | 0.01 |
| 13. | Sodium salicylate+ibuprofen | (10) | | 18.3±3.82 | 0.01 |
| 14. | Sodium salicylate+paracetamol | (10) | | 12.3±3.05 | 0.01 |

All are statistically significant.

Groups 2 to 8 were compared with group no. 1.

Groups 9, 10, 11, 12, 13 & 14 were compared with groups no. 2, 3, 4, 5, 6 and 7 respectively.

*(IV) Measurement of total acidity*

It was found that total acidity was reduced significantly by all the drugs included in this study and by drug combination with sodium salcylate (Table II).

## DISCUSSION

The results show that aspirin, indomethacin, phenylbutazone and sodium salicylate are highly gastric ulcerogenic. These results are in agreement with those of other workers (3,7,11,13,16). Paracetamol and ibuprofen were found to be free from ulcerogenic action in guinea pigs. However, other workers have reported that ibuprofen also possesses ulcerogenic action (3). The discrepancy may be explained on the basis of species variation.

The prior treatment of animals with sodium salicylate did not modify the gastric ulcerogenic action of aspirin (microfined and ordinary), but it antagonized the ulcerogenic action of indomethacin. This is in agreement with the results reported by others (3). It has been observed that sodium salicylate antagonizes the action of indomethacin only while others (3) have reported that sodium salicylate antagonizes the action of indomethacin, ibufrofen and phenylbutazone, Our results show that sodium salicylate potentiates the ulcerogenic action of phenylbutazone, ibuprofen and paracetamol in guinea pigs. The difference may be due to species variation.

The significant reduction in total acidity by all the drugs included in the study, may be due to loss of hydrogen ion from the back diffusion through mucous membrane barrier (6,8,9,12,14,15).

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