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Antinflammatory Property of New Pyrazolon Derlivatives

Reginaid N.P. Nwankwoala, Owunari A.georgewill and Udeme O. Georgewill

Departments of Pharmacology and Toxicology Faculty of Basic Medical Sciences
College of Health Sciences University of Port Harcourt, Rivers State, Nigeria.

Abstract: The anti inflammatory effects of 4-trifluoroacety1-1- pheny1-3- methy1 pyrazolone (HTFP) and 4-sebacry1-bis 1-pheny1-3- methy1 pyrazolone (HSP) were investigated and compared with those of phenylbutazone (PTZ) using carrageenan-induced paw inflammation model in rats. Different doses of PTZ, HTFP and HSP were intra-peritoneally administered to rats and one hour thereafter, inflammation was induced by injecting carrageenan into the left foot of the rat. The right foot received saline. Five (5) rats received carrageenan and saline only. Both the left and right feet were measured hourly for four hours. PTZ, HTFP and HSP significantly reduced carrageenan induced inflammation. 100mg/kg PTZ caused 62.5 ± 5.25% reduction of the inflammatory response whereas 10mg/kg HTFP and 10mg/kg HSP reduced inflammatory response by 53.6 ± 5.0% and 32.5 ± 4.50% respectively. Thus anti-inflammatory properties of these drugs were less at lower doses. These results show that

(1) HTFP and HSP possess anti-inflammatory property,
(2) HTFP is more potent than HSP and
(3) The anti-inflammatory potency of phenylbutazone drug is greatly enhanced by substitution of trifluoroacety1 -1- group at position 4 of the pyrazolone molecule.

Key words: pyrazolon derivative, HTFP, HSP CARRAGEENAN-INDUCED-INFLAMMATION

INTRODUCTION

From therapeutic view point, phenylbutazone (PTZ) is the most important member of pyrazolon group of drugs. PTZ is used for the treatment of acute gout and rheumatoid arthritis and allied disorders [1,9,2,4]. It is an effective anti-inflammatory agent but serious toxicity limits its use in long term therapy[9,4]. These toxic effects include peptic ulcer (or its reactivation) with hemorrhage or perforation, hypersensitivity reactions of serum sickness type, ulcerative stomatitis, hepatitis, nephritis, a plastic anemia, leucopenia, agranulocytosis and thrombocytopenia[9,2]. These toxic effects have therefore evoked the search for more potent or equally potent derivatives of pyrazolon with less toxic effects than PTZ. The consequence of this search is the synthesis of two new drugs which are a modification of PTZ nucleus namely: 4-trifluoracety1-1- pheny1-3-methylpyrazone (HTFP) and 4-sebacry-bis-1- pheny1-3-methy1 pyrazone (HSP).

These new derivatives of pyrazolon are now subjected to pharmacological tests in order to assess their pharmacological properties in relation to the older drug PTZ. This is what informed us to test for the anti-inflammatory effects of these drugs.

MATERTALS AND METHODS

Animals: 5-10 weeks old albino Wister rats of both sexes weighting 100g -150g were used. The animals were obtained from the animal house of University of Port Harcourt and kept in the departmental animal house at least 7 days before use. They were fed on chicken mash supplied by super feeds Nigeria Ltd, and were given drinking water ad libitum.

Drugs and Reagents: PTZ and carrageenan were obtained from sigma chemical U.K. 1% carrageenan solution was prepared by dissolving 1 gram of carrageenan in 100ml of saline. HTFP and HSP were supplied from the department of chemistry, university of Port Harcourt.

Methods:

a.induction of Inflammation: inflammation was induced by injecting O. 1ml of 1% carrageenan solurion into the foot of the rat[8].

Experiments: The experiment was divided into two groups viz: one control group and the drug treated group. The control rats consisted of five (5) rats and

Corresponding Author: Reginaid N.P. Nwankwoala, Departments of Pharmacology and Toxicology Faculty of Basic Medical Sciences College of Health Sciences University of Port Harcourt, Rivers State, Nigeria.

these received intra -peritoneal administration of O. 1ml of 1% carrageenan into the left foot whereas the right foot was given O.1ml saline. The paw size was subsequently measured hourly for four (4) hours.

In the drug treated group, the following doses, 100mg/kg, 10mg/kg PTZ, 10mg/kg 1mg/kg HTFP and 10mg/kg HSP were administered intra pertoneally one hour before the induction of inflammation in the rats. Each dose was given to 5 rats. One hour after administration of the drugs, 0.1m1 of 1% carrageenan was given to the left foot whereas 0. 1m1 of 1% saline was administered to the right foot. The Paw size was then measured hourly for four (4) hours. Percentage of anti-inflammatory response was calculated from the

formular; % Antiinflammatory Response $= \frac{A-B}{A} \times 100$ where

A= Paw size of the control animal.
B= Paw size of the treated animal.

Student's t-test was used to test for statistical significance.

A.P. value of 0.05 was considered statistically significant.

Where indicated, the anti-inflammatory responses were reported as means ± standard error (SE).

RESULTS AND DISCUSSION

As shown in Table 1 PTZ, HTFP and HSP demonstrated anti-inflammatory property. Four (4) hours after the induction of inflammation, 100mg/kg PTZ significantly reduced (P 0.05) inflammatory response by 62.5 ± 5.3%. Similarly 10mg/kg HTFP and 10mgkg HSP caused a significant reduction (P 0.05) of inflammatory response by 53. 6 ± 5.0% and 32.5 4.50% respectively.

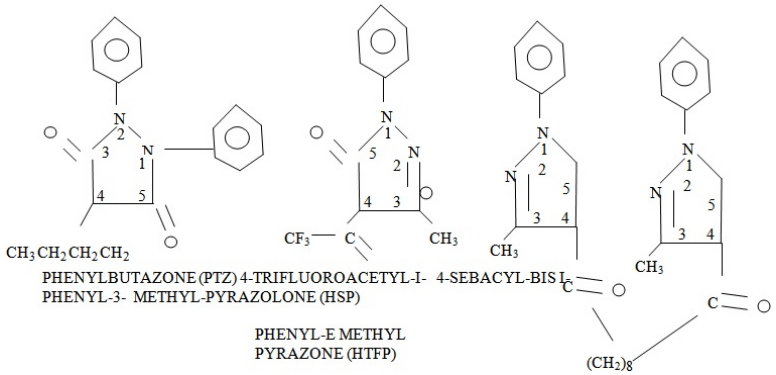
Table 2 shows that 10 mg/kg PTZ caused a significant reduction (P.0.05) of inflammatory response, decreasing the response by 32.5 ± 5.3% from the control values. Similarly 1mg/kg HTFP caused a significant reduction (P0.05) of inflammatory response by 27. 3%. On the other hand, 1mgkg HSP reduced the inflammatory response by 17.5 ± 4.5% and this reduction was not significantly different (P0.05) of inflammatory response by 17.5 ± 4.5% and this reduction was not significantly different (P 0.05) from the control.

Finally, 10mg/kg HTFP significantly reduced (P 0.05) carrageenan induced inflammation much more than that produced by HSP. The anti-inflammatory response produced by 10mg/kg HTFP (53.0 ± 5.0%) was not significantly different (P 0.05). from that produced by 100 mg/kg PTZ (62.5 ± 5.3).

Table 1: Effect of ptz, htfp and hsp on carrageenan induced inflammation.[a]

DRUG	CONCENTRATION MG/KG	% INHIBITION OF INFLAMMATORY REACTION.
PTZ	100.00	62.50±5.30[b]
HTFP	10.00	53.60±5.30[b]
HSP	10.00	32.50±4.50[b]

[a]All values are Mean ± S. E. M. of five determination,. The anti-inflammatory reaction was quantitated as described in the methods and the results are expressed as percentage of inflammatory reaction in the control animal.
[b]P 0.05 as compared to the control.



Discussion: PTZ is effective anti-inflammatory agent [5,9,2,7]. The results of this study confirm this property of PTZ and also assert that the derivatives of this drug namely HTFP and HSP also posses anti-inflammatory property. The anti-inflammatory property of PTZ is comparable to those of HTFP because 100mg/kg PTZ reduced the carrgeenan induced inflammatory response by 62% whereas 10mg/kg of HTFP reduced the inflammatory response by 53%. HSP possesses anti-inflammatory property but to a less extent when compared with HTFP.

In this study, at both 10 mg/kg and 1mg/kg doses, HTFP demonstrated more anti-inflammatory response than HSP. Structurally, HTFP differs from HSP by

possessing trifluoroacety1 group (Fig. 1). Therefore the results of this study suggest that the anti-inflammatory potency of the pyrazolon drug is greatly enhanced by substituting trifluoroacety1 group at position four (4) of the pyrazolon molecule.

As stated above, the usefulness of PTZ is limited because it causes many serious toxic effects[2,7,6]. Having established that these drugs possess anti-inflammatory property comparable to that of PTZ this study thus evokes more investigation on the toxicity of these provolone derivatives in order to determine their level of toxicity. The toxicity studies are currently being carried out in our laboratory.

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