ANTI-INFLAMMATORY PROPERTY OF RANITIDINE, A SPECIFIC H_2-RECEPTOR ANTAGONIST

M. D. PATWARDHAN, M. P. MULEY AND M. S. MANEKAR

Department of Pharmacology,
Govt. Medical College, Miraj - 416 410 (MS)

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Summary : The effects of ranitidine (2 *mg/kg*, po) and phenylbutazone (100 *mg/kg* po) have been studied in different models of acute and chronic inflammation in rats. Ranitidine showed significant anti-inflammatory activity in the four models used. This observation supports the concept that histamine has a pro-inflammatory role that is mediated via stimulation of H_2-receptors.

Key words : ranitidine phenylbutazone anti-inflammatory

INTRODUCTION

Since Dale and Laidlaw's original observation in 1919 (4) that the local actions of histamine are similar to the inflammatory response, the possible involvement of histamine in inflammation is discussed extensively (12, 13). Pelczarska (11) reported that hypostamine, a histidine decarboxylase inhibitor reduced the inflammation and oedema associated with rat adjuvant arthritis. However, the 'classical' (i.e.H_1) antihistamines did not affect the severity of rat adjuvant arthritis even at very high dose levels (2). The failure of the classical antihistamines to suppress many other inflammatory conditions has led investigators to suggest only a minor inflammatory role for histamine in acute inflammation (16). However, many actions of histamine which are resistant to the classical H_1 antihistaminics, have been shown to be blocked by the histamine H_2-antagonists (3). Our earlier observations (10) have suggested the involvement of both H_1 and H_2 receptors in the local actions of histamine i.e. triple response. Hence it was thought worthwhile to study the role of H_2-receptors in different models of acute and chronic inflammation using the new, specific H_2-receptor antagonist, ranitidine.

MATERIAL AND METHODS

Albino rate (Haffkine strain) of either sex (100-200 *g*) were used. For each set of

experiment, the rats were divided into three groups, each group containing at least six animals.

For the acute experiments, the rats were fasted for 18 hr, but water was allowed *ad-lib*. For the chronic experiments, the animals had free access to food and water throughout the seven days period. The drugs were given orally. Control animals received distilled water while the other two groups received solution of ranitidine hydrochloride (Glaxo Group Research Ltd; 2 *mg/kg*, po) and phenylbutazone (SG Pharmaceuticals; 100 *mg/kg*, po, as a suspension in 4% gum acacia). For the acute experiments, the animals received distilled water or drugs one hr prior to the injection of carrageenin, turpentine or formalin. Students 't' test was used for statistical analysis.

a) *Carrageenin-induced oedema :* The method of Winter, Rislay and Nuss (15) was followed with slight modifications. Drugs or distilled water were given one hr before injecting carrageenin. 0.1 *ml*. of 2% carrageenin in 0.9% saline was then injected underneath the plantar aponeurosis of the left hind paw of the rat. The foot volume was measured by plethysmograph in the rats anaesthetised with ether, before and again 3 hr after carrageenin injection.

b) *Turpentine-induced arthritis :* Joint oedema was provoked by injection of 0.01 *ml* turpentine oil into the synovial cavity of the right knee joint with the help of a tuberculin syringe (7).

Knee joint lateral diameter was measured using vernier callipers measuring to 0.02 mm by the method described by Al-Haboubi *et al.* (1). The mean increase in joint diameter after 6 hr was compared in the two drug treated groups.

c) *Formalin-induced peritonitis :* The method adopted was that of Teotine *et al.* (14). The animals were treated with the respective drugs or normal saline and after one hr., all animals received 1 *ml* of 1.33% formalin (ip). After 6 hrs, the animals were sacrificed, abdomen cut open and the volume of exudate was measured.

d) *Cotton wool pellect granuloma method :* The method of Meier, Schuler and De Saulles (9), as described by Finney and Somers (5) was adopted with slight modifications. A sterile cotton pellet weighing 10 *mg* was inserted, one in each flank. The test drugs were administered orally daily for seven days. The pellets were dissected out on the eighth day, dried in the oven till their weights remained, constant, and then weighed.

RESULTS

Table I shows the effects of ranitidine and phenylbutazone in modele of acute

inflammation (carraeenin-induced oedema, turpentine-induced arthritis and formaline-induced peritonitis). As is obvious, ranitidine decreased the formation of inflammatory exudate in all three models and the resulrs were almost similar to those of phenylbutazone, though in the formalin-induced peritonitis it is slightly less effective.

A similar effect of ranitidine was also seen in the cotton pellet granuloma model which is a model of chronic inflammatory activity (Table I).

TABLE I : Effect of ranitidine and phenylbutazone in various models of inflammation in rats.

Model and parameter	*Pre-treatment*		
	Distilled water (controls)	*Ranitidine 2 mg/kg, PO*	*Phenylbutazone 100 mg/kg, PO*
a) Carrageenin pedal oedema (paw volume, *ml*)	4.79±0.19 (12)	2.50±0.19*** (9)	1.84±0.12*** (12)
b) Turpentine arthritis (Knee joint, lateral diameter, *mm*)	2.59±0.17 (10)	1.44±0.13* (8)	1.49±0.19* (8)
c) Formalin peritonitis (Volume of exudate, *ml*)	7.26±0.23 (12)	2.78±0.6*** (12)	1.22±0.10*** (11)
d) Cotton pellet granuloma (granuloma tissue, *mg*)	57.61±0.49 (8)	36.29±0.52*** (12)	36.72±0.35*** (16)

1. All values are mean ±S.E.M. Parentheses show number of rats in a group.
2. Value differs significantly from control. * $P<.05$, *** $P<.001$.
3. Treatment was given once in (a), (b) & (c) and for 7 days in (d) See text for methodology and drug administration schedule.

DISCUSSION

Folkow *et al.* (6) suggested the presence of two types of histamine receptors responsible for histamine induced vasodilatation. Only one of these could be effectively blocked by benadryl and the related compounds. This second type of receptor is labelled as H_2-and the new H_2-receptor blocking agents have been established to block those actions of histamine which were not blocked by the classical antihistaminics (3). New evidence implicates histamine as a possible mediator in a number of pathological conditions involving increase in vascular permeability and oedema. This action of histamine is

mediated through H_2-receptors. Metiamide and cimetidine have been reported to suppress irradiation or thermal oedema (8). Al Haboubi and Zeitlin (1) have observed the anti-inflammatory activity of cimetidine in rat adjuvant arthritis model. Our previous observations (10) also suggest a role for H_2-receptors in the local actions of histamine.

In concurrence with these reports, in the present study, ranitidine was found to significantly reduce the inflammatory response in different models of acute and chronic inflammation. This anti-inflammatory response was comparable to that of phenylbutazone in doses used, in all the models of inflammation used, except one i.e. formalin-induced peritonitis. However, we have not undettaken a systematic comparison in relative potencies. This report further supports the concept that histamrne does have a proinflmamatory role mediated via stimulation of H_2-receptors.

The dose used in these experiments is higher than that is required to reduce gastric acid secretion. It would be worthwhile to find out whether low doses of ranitidine can produce synergistic effect with anti-inflammatory drugs. This would be particularly advantageous since H_2-receptor antagonists would also counteract their limiting side effect i.e. peptic ulceration while adding to their therapeutic effect.

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